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(54) Title: METHOD AND APPARATUS FOR DETECTION OF A CONTROLLED SUBSTANCE
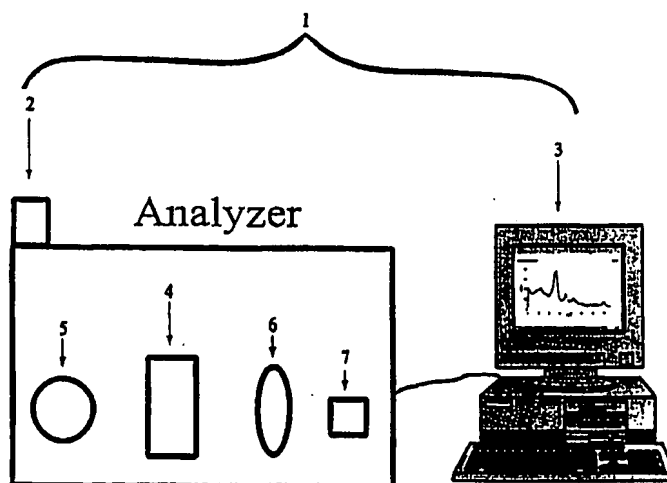
(57) Abstract

Techniques and devices for detecting and analyzing controlled substances and the like are discussed including highly reactive sensor molecules which are coated on a spectroscopic sample surface (4) and which may chemically react with a given analyte to form a covalently bonded adduct with spectral characteristics unique to the new adduct. The techniques provide the basis of a detection system with high sensitivity and high specificity in which the surface can even be washed to remove interfering or nonreactive compounds. The sensor molecules which comprise the coating (8) may have three major components: a central molecular scaffold ("CMS"), a "tether" terminated by a surface attachment group "SAG", and a reactive functional group "RFG" which may be highly reactive towards certain classes of molecules. One or more modifiers or modifier groups "Z" which may serve to increase or decrease the reactivity of the RFG towards target analytes, or to modify the spectral characteristics of the adduct may also be included. Some sensor molecules include diazonium compounds, activated acyls, and nitrosos.

METHOD AND APPARATUS FOR DETECTION
OF A CONTROLLED SUBSTANCE

I.   TECHNICAL FIELD

5   Generally this invention relates to the field of detecting the use of controlled substances

such as illicit drugs and the like. More specifically, the invention involves the field of

Raman spectroscopy to accomplishing detection and the sub-field known as Surface

Enhanced Raman Scattering. In a less focused sense, this invention relates to a method of

detecting substances through the use of a coated surface and spectroscopic techniques. The

10   invention also covers the use of a new coating with a tethered reactive species that

chemically binds to an analyte. Through this new technique, the analyte is then

spectroscopically analyzed as part of a new chemical species which is the reaction product

of the analyte and the reactive species.

15 II.   BACKGROUND ART

        The field of sensing controlled substances is an area which has evolved primarily for the

public good. As practically everyone knows, drug and alcohol abuse are significant

problems for society. In fact, in 1998 the United Nations conducted an international anti-

20   drug conference involving over one hundred nations which are facing this societal

challenge. As society attempts to address this problem it has turned to increasingly

sophisticated technical analysis to counter the abuser's attempt to hide either the controlled

substance or its use. Naturally, the principles of analytical chemistry have been relied upon

for their ability to not only detect but to discriminate the presence of a controlled substance

25   in minute amounts. Unfortunately at its present state, the field of detecting controlled

substances still has difficulty in both sensing and discriminating the existence of some

substances as well as in avoiding false positive indications. This invention provides a

solution that greatly expands the techniques and accuracy available for a variety of

substances. It also provides a framework under which practical advantages can now be

30   achieved. These advantages range from the seemingly simple ability to provide a single

sensor for a variety of drugs as well as the ability to now be able to discriminate between

controlled substances and some chemically similar uncontrolled substances. This latter

aspect can be significant because in a variety of applications such as Olympic drug testing

and the like, it has become difficult to accurately sense and distinguish the difference between certain substances which are legally available for use and those which are truly illegal substances. In a broader sense, the invention also provides an expansion to the principles of analytical chemistry since it may be applied in other areas as well.

5   The field of analytical chemistry dates back at least to Pliny the Elder (AD 23-79) who first described the use of an extract from gallnuts that turns black in the presence of iron sulfate. This allowed him to determine if copper sulfate was contaminated with iron sulfate. This simple concept of chemical analysis has grown into analytical chemistry which is one of the four disciplines of modern chemistry. Analytical chemistry encompasses a variety of

10   fields such as clinical chemistry, environmental chemistry, geochemistry, and forensic chemistry. The techniques of analytical chemistry have grown from the simple wet chemical analysis discovered by Pliny the Elder to very sophisticated instrumental methods. Early analytical chemistry relied on visual observation of color changes or the precipitation of a compound to quantitate materials. This meant that the sensitivity was often limited to

15   the visual acuity of the chemist. Instruments have largely replaced these visual techniques, since it is possible to electronically detect changes in light intensity and wavelength with vastly superior sensitivity.

The electronic detection of changes in light intensity and its separation into different

20   wavelengths is the basis of the field of analytical spectroscopy. This is an area in which some type of analyte, namely, some substance or chemical which is desired to be studied, is exposed to some wavelength of energy. This wavelength may be a singular wavelength such as a laser often provides, or it may be many different wavelengths. To provide the information desired, the analyte then causes some type of change in that incident energy and

25   thus results in some type of change in intensity of at least one wavelength of energy which is characteristic of the analyte. Thus the wavelength of energy to which the analyte is exposed and the changed signal resulting usually vary. Naturally, the incident energy may be present in a variety of forms as those aware of the wave-particle duality may easily understand. Essentially, however, all that spectroscopy involves is an incident wavelength which is

30   somehow affected by an analyte to result in a changed signal. This signal may be a singular

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wavelength or may be a broad spectrum of wavelengths of emission or adsorption. Thus, "spectroscopy" as intended here is not intended to be limited to only some type of slit-based instrument, but rather is intended to fully encompass the areas of analytical chemistry in which changes in wavelengths of energy are studied to gain information with regards to an analyte. Conversely, it should be understood that other fields or areas of study which do not

5   involve changed wavelengths have not been viewed as particularly relevant to this field. For example, the areas of chromatography and the like which act to separate substances, immunoassays which transiently bind substances for nonspectroscopic purposes, and the like, have not been viewed as particularly relevant to the fields in which this invention relates.

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As mentioned earlier, the field of sensing controlled substances faces a variety of limitations. These range from imperfect discrimination (such as in the Olympic drug testing scenarios) to practical challenges such as the need to have different tests for different substances. When considering spectroscopic techniques, great improvement has occurred

15   through the introduction of a technique known as Raman spectroscopy. Raman spectroscopy was discovered by Sir Chandrasekhara Venkata Raman in the early 1900s who found that different chemicals sometimes caused unique scattering of an incident wavelength of energy. Since the scattering was largely unique to each chemical, the analysis of the specific scattering thus provided information from which specific chemical detection

20   and identification could be achieved. Unfortunately, limits remained even with the introduction of Raman spectroscopy.

In 1976, a new spectroscopic technique was discovered that is sensitive to interfaces. This technique has been coined Surface Enhanced Raman Scattering (SERS). SERS tends

25   to give large enhancements of Raman scattering in the presence of certain prepared metallic surfaces. The SERS technique has been applied to a variety of problems -- not only those associated with analytical chemistry -- and more recently has been the subject of several publications and patents for analytical chemistry. This technique generally involved some type of attachment of an analyte to a metal surface or to a coating on a metal surface such as

30   gold or silver.

Even in the broader area of general analytical chemistry, initially, the coatings were not tethered to the metal surface. In U.S. Patent No. 5,327,211 relating to analytical chemistry in general, Carron and Mullen showed that it was possible to coat a surface with a dye that had complexed with a metal ion to serve as a metal ion detector. Again in the broader field of analytical chemistry, Angel was awarded an early patent, U.S. Patent No. 4,781,458 for

5 the determination of analytes adsorbed directly to metals surface or partitioned onto a coating. Even more recently some publications by Carron and U.S. Patent No. 5,327,211 disclosed the use of SERS with coatings that contain thiols to tether the coatings to a silver surface. That disclosure specifically addresses the use of SERS coatings on a fiber optic to allow for remote sensing. Carron, et. al, has demonstrated that the coatings mimic

10 separation science coatings and also serve to stabilize the SERS substrate to give it longevity. The coatings can also provide an internal standard that allows one to use relative intensities to determine a calibration that can be used to find the concentration of the analyte.

15 The general techniques of SERS has been well established and is discussed to some degree not only in the above general analytical chemistry references, but also in a variety of references ranging from text books to additional patents such as U.S. Patent Nos. 5,693,152 to Carron, 5,255,067 to Carrabba, and Nos. 5,266,498, 5,376,556, and 5,567,628 to Tarcha in the immunoassay field. To the extent necessary, each of these references is hereby

20 incorporated by reference to provide additional understandings as they relate to the Raman and SERS techniques generally.

One of the perspectives that has evolved to those focusing on these techniques has been a perspective that suggests that it may be more appropriate to avoid changing any structures or

25 spectral characteristics of an analyte during its spectroscopic analysis. This perspective seems rooted in the understanding that, naturally, if one wants to detect the analyte itself, it would be better not to alter the analyte or controlled substance. Thus, the coatings developed to date for analytical applications of SERS have been coatings that weakly interact with the analyte to produce a reversible measurement of the analyte concentration.

30 These include alkylthiols that mimic the nonpolar coatings used in reverse phase HPLC, pH

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and metal sensitive coatings that mimic ion chromatography, and oxide coatings that mimic normal phase chromatography.

By weakly interacting with the analyte to produce a measurable spectrum, the goal of seeing only the analyte spectrum had been satisfied. As a result, the techniques of Raman

5 spectro- scopy and specifically that of Surface Enhanced Raman Scattering, had to some degree been viewed as limited since the surfaces typically used in SERS have been the relatively unreactive substances of gold and silver. Since these substances can cause the desired weak interactions in only a few situations, these techniques, while powerful for certain analytes, had not been as greatly exploited as possible in the field of detection of

10 controlled substances. In essence, since a goal was that the surface itself created some sort of weak link with the controlled substance, and since not many controlled substances would establish an appropriate link with the typically required gold or silver surfaces, these techniques were often not viewed as particularly appropriate to the field of detection and analysis of controlled substances or specific substances and the like. The techniques were

15 also viewed as somewhat limited themselves because it seemed that they could really only be used for those specific types of analytes that happened to bond appropriately to the required surface. Although eventually different sample surfaces did exist for certain different analytes, generally the selections were so limited that the techniques were perhaps underutilized.

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One example of efforts to alter the surface involved in the SERS technique is disclosed in U.S. Patent No. 5,693,152 to Carron, one of the present inventors. In that patent, Carron disclosed a technique to modify the surface enhanced Raman scattering (SERS) detector by applying a stabilizing coating on the SERS surface. The coating applied would reproduce or

25 mimic the specific separation procedure being utilized thus this method could be used universally for all types of analytes and separation methods. Similar to the invention disclosed in a patent by Carrabba et al (U.S. Patent No. 5,255,067), a roughened surface substrate was used to improve SERS detection efficiency in gas chromatography. However, although the coating disclosed in '152 patent can locally increase the analyte concentration

30 and improve linking affinity between the coating and the analyte, the attachment of these

analytes to the coatings are still through weaker linking mechanisms, primarily by means of adsorption or other weak forces.

Similarly, other, perhaps unrelated fields have seen efforts to alter binding sites in the immunoassay area. As mentioned earlier, the use of SERS technology for immunoassays

5   has been disclosed by Tarcha et al. in U.S. Patents No. 5,266,498, 5,376,556, and 5,567,628. In their disclosures the authors designed a Raman active reporter which is bound to a specific binding member. However, this is not only an immunoassay method, it involves attachment of an analyte to a binding member through weaker techniques and thus even though it is in an unrelated area, seems to show the pervasiveness of the perspectives

10 and attitudes of those involved in Raman spectroscopy.

In the focused field of detecting controlled substances, however, the problems seem even more acute. Those involved in sensing controlled substances (and other, even uncontrolled substances) have faced problems with the discrimination abilities between substances. The

15 problems for professional athletes who may have taken some type cold medicine prior to their participation in the Olympic games has been highly popularized. From one perspective this problem may be viewed as a simple byproduct of the inability of the analytical techniques to adequately discriminate between a legal cold medicine and the remnants as a result of the use of an illegal drug.

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Another problem which is the fact that it is desirable to sense controlled substances in extremely low concentrations. Again, the seemingly irresolute requirement that the analyte or controlled substance only weakly binds with the spectroscopic surface has made it challenging to sense such low concentrations because the equilibrium values are often such

25 that the analyte would desorb from the surface and not permit a sufficient build up to facilitate high quality detection. Further, a problem has existed in instances in which it was desired to not only detect but to quantify the presence of either some controlled substance or more generally an analyte, over a broad ranges of concentrations. In those instances in which such spectroscopic techniques were found to apply, it was often the case that the

30 ranges over which a specific sensor could be used made it practically difficult to achieve the

technique.

Furthermore, because there are a great variety of controlled substances, one of the problems has been in the ability to use the specific spectroscopic technique to sense not only one specific type of controlled substance but to sense a great variety of substances. Not only

5 have there existed limitations on which specific substances interact appropriately with which specific sensors, but there have existed seemingly fundamental limitations such that certain substances could not be analyzed through Raman techniques. Naturally, while many of these problems are particularly acute in the focused field of sensing controlled substances, it can be easily understood that these problems also applied to more general

10 applications of spectroscopic techniques as well.

One way in which the apparent requirement of a weak interaction has resulted in a difficulty is the practical fact that interfering substances are often present. While it would be desirable to remove these interfering substances, the weak interaction has made it more

15 difficult to remove the interfering substances without also removing some analyte as well. Even the improved SERS coating disclosed in U.S. Patent No. 5,693,152 highlights that this problem continued unsolved. Essentially, the problem was that while such a SERS coating could specifically adsorb material from the matrix, there were no ways of washing the surface to remove the interferences either unavoidably or practically present in the matrix.

20 Furthermore, since the interaction of the analyte with the surface was often viewed as necessarily reversible, it was implied that the interaction needed to be weak. Physically, this often meant that only a small amount of the analyte tended to interact with the surface or could be detected in a given instance.

25 Thus, in the field of sensing controlled substances, there has been a long felt but unsatisfied need for a detection technique which could be applied to a great number of controlled substances and which could also provide a higher degree of discrimination between such substances especially those which were not considered illegal. Even though those skilled in the field of sensing controlled substances appreciated this desire, they

30 seemed not to have fully appreciated the nature of the problem in that their perspective was

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driven by certain preconceptions which actually limited their ability to solve the problems
with which they were faced. To some degree their substantial attempts failed to fill the need
either because their field did not require the basic physical understanding of the
phenomenon or they simply assumed that existing techniques could not be adapted to their
unique needs. For this reason, it appears that those skilled in the art to some degree actually
5   taught away from the direction in which the present inventors went.

As related to the broader field of analytical chemistry in general, it appears that similar
perspectives also apply. For instance, while those in the field of analytical chemistry in
general well appreciated that it was desirable to apply sensitive techniques such as Raman
10 spectroscopy and the SERS techniques to a greater variety of substances, their apparent
tendency was to approach the problems from the perspective of seeing primarily the analyte
as opposed to some altered by-product. Again, while they had expended substantial efforts
to expand the applicability of the techniques, their focus toward physisorption perhaps
showed that they did not fully appreciate the nature of the problem. They seemed thus to
15 teach away from the direction in which the present inventors went pursuing avenues that in
hindsight might be viewed as based on misperceptions to some degree. Not only were these
misperceptions fostered by the initial desire to sense an unaltered analyte, but they also were
fostered by attitudes which seemed to suggest that reversible and remote sensing
arrangements were required for some practical reason. Thus, to some degree the present
20 invention might even be characterized as unexpected in the sense that it proposes techniques
and substances which, prior to this invention, were not just deemed suboptimal but rather
were viewed as contrary to the goals typically considered and the results typically desired.

In addition to the aspect of applying analytical techniques to a greater variety of
25 substances, those generally applying the techniques had long felt a need for an ability to
apply those techniques to greater ranges of concentrations and to greater varieties of
chemicals during one analysis event. Even though a desire existed, they may not have fully
appreciated that the problem and solution lay not in sample preparation or non-
spectroscopic techniques, but in adjustments to the analytical technique itself or to the
30 specific sensors involved in the analytical technique. Efforts focused in a direction different

from those of the present inventors may have been due to the fact that those involved did not

to some degree fully appreciate that sensor chemistry could offer the needed advances and

simplifications.

III.   DISCLOSURE OF THE INVENTION

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       To address these and other problems, the present invention involves techniques and

devices which offer improved spectroscopic analysis capabilities. As applied to the field of

sensing controlled substances, the invention involves the creation of a unique surface

coating such as a diazonium or other type of coating which interacts with the substance in a

10 wholly different manner. Rather than forming the weak interactions that were previously

viewed as perhaps required, the invention creates a whole different type of interaction,

namely a full reaction such as in the formation of a covalent bond to produce an entirely

different species, termed here an adduct. Since in most instances the formation of this

covalent bond is irreversible, the rate of loss of the controlled substance or other analyte

15 from the surface will be approximately zero. As a result, washing or other steps to remove

interference substances can now be accomplished. Thus, as a result, the invention offers a

greatly expanded Surface Enhanced Raman Scattering technique through which coatings

may be altered as appropriate for specific substances and through which expanded ranges

and sensitivities can now be accomplished. Thus the detection of substances which are

20 controlled, substances of a medical nature, or simply some new types of analytes are now

possible. In its approach, the invention breaks with what may have been preconceptions and

utilizes a substance, such as diazonium, which is highly reactive with the controlled

substance or other analyte at issue. Thus the diazonium and the like may interact to

permanently bond or perhaps covalently bond with the analyte as opposed to the more

25 typical weak chemisorption or physisorption. Through this reaction the diazonium may be

viewed as an advantage rather than a hindrance in that an actual adduct is created and rather

than studying the analyte in isolation the resulting adduct is studied.

       In a more basic form, the invention includes a method of detecting molecules by

30 chemically binding them to a surface and then using a surface-sensitive detection method.

This is a significant improvement over the existing method of attracting molecules to a surface through weak forces. The new technique increases the sensitivity of detection by forming a strong bond between the analyte and the surface coating. The equilibrium between surface analytes (e.g. detectable analytes) and solution analytes (e.g. not detectable since not captured by the surface) may be characterized by an equilibrium constant. In one

5 sense, the equilibrium constant describes the number of species at the surface relative to solution. In another sense, it describes the rate at which molecules go on the surface relative to the rate at which they come off. The present invention describes a method of forcing the off rate to be essentially zero and to thereby greatly increase the number of species on the surface (e.g. the detectable species). This is one form of sensitivity improvement. A

10 second method of improvement comes from the ability to wash the surface after the analyte has bonded to the surface. In many cases, the sensitivity of an analytical method has been limited due to the presence of large interfering backgrounds. This background arose from species in the solution with the analyte that gave rise to a signal that was similar to that of the analyte. These interfering species can now be removed with this invention since the

15 analyte is bound to the surface and the interfering species can be easily washed off without affecting the analyte. (This, of course may, not work for every analyte possible.) A third method of improvement comes from the ability to distinguish between different analyte types. Because the adduct formed through formation of a covalent bond is a new and unique chemical species, it will likely have unique spectroscopic characteristics. Since

20 different analytes will form different adducts, they may be distinguished from each other on the basis of the differing spectra, thus decreasing the likelihood of mistaken identification.

In the field of sensing controlled substances, it is thus an object of the invention to provide techniques and devices which may be applied to a greater variety of controlled

25 substances and which may be applied to all substances with a higher degree of sensitivity, with greater ability to discriminate, and even with the possibility of confirmational systems to be automatically in place to avoid false indications. In keeping with these objects, it is a goal of the invention to offer a system which is controlled to a lesser degree by the equilibrium constants of a reaction and which even offers situations where the equilibrium

30 constant is essentially zero. Similarly, a goal is to provide a system in which interfering

substances and the like can be removed without concern of removing or somehow reducing

the signatures available as a result of the controlled substance itself. A further goal is for a

system which permanently binds the controlled substance to the sensor surface and thus can

be analyzed at any location or any time without a high degree of concern of degradation of

the signal.

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A more broadly stated goal for the invention in the field of sensing controlled substances

is that of providing techniques which can be designed for specific chemicals in specific

situations. Thus a goal is to provide a system which can be optimized through chemical

design for either specific substances or for specific ranges and broader substances in one

10 analytical event.

An object as it relates to the broader field of analytical chemistry in general, as well as in

the field of detecting controlled substances, is to provide a system in which internal

standards can permit the monitoring and compensation for alterations in the illumination

15 source as well as to provide techniques in which coatings rather than the surfaces

themselves can be used in a variety of detection techniques. Thus, the invention could be

used with a large variety of analytical techniques, known to those in the art. Optical

techniques such as Raman, fluorescence, or absorption spectroscopy could be used for

detection. Mechanical detection would also be possible with sensitive mass sensors.

20 Raman scattering may prove to be one of the most desirable detection methods. Surface

Enhanced Raman Scattering (SERS) provides large enhancements in the Raman scattering

from molecules near certain metal surfaces. The invention thus involves methods of

anchoring our molecule specific probes to this type of surface. Moreover, while the

invention contains a fairly high specificity for specific classes of molecules it may not need

25 to be truly specific to a single molecule. SERS, of course, is a truly molecular-specific

detection method. This means that a complex mixture of species in a reactive class of

compounds could react with the surface and SERS could differentiate and quantitate

between the various species.

30   The use of SERS also provides a substantial improvement over many techniques through

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the use of an internal standard. The internal standard furnished by this invention can be the
' portion of the surface tether that is unchanged by the reaction of the reactive functional
group (RFG) with the analyte. This portion of the surface coating may give rise to a SERS
signal that can be monitored simultaneously with that of the analyte. A simple ratio of the
two signals or a more sophisticated multi variate analysis can be used to give a detection
5   method that is independent of source intensity fluctuations or variations in the detection
throughput. This creates the possibility for more simplified and less expensive instrument
design as well as design for rugged, maintenance free use.

IV. BRIEF DESCRIPTION OF DRAWINGS
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FIG. 1 shows spectra of a prototype coating, 4-amino phenyldisulfide, and its reactivity
toward phenols. A) A SERS spectrum of 4-amino phenyldisulfide. The disulfide bond has
broken and the surface species is 4-amino thiophenylate. B) A SERS spectrum of the
coating used in Figure A after treatment to make it into a diazonium salt. C) A SERS
15   spectrum of the coating in Figure B after exposure to phenol. The Raman features around
1512 cm-1 are indicative of the azo functionality. The shows that the coating reacted with
phenol to make an azo compound.

FIG. 2 is an example of the components that might be present in the instrument required
20   to read the results of the current invention. The input may be for a sample entry, the source
may be some sort of light source, the sample compartment may be where the measurement
is made after reacting with the coating, the optics may be used to transfer and modify the
signal prior to detection, the detector may be a transducer that converts an optical signal into
an electrical signal that could be read by a computer, and the output may be a computer that
25   converts the electrical signal from detector and performs analysis on the data to produce a
result. The result may be a simple detection, a quantitation, or even a full identification of
the amount of analyte in the sample.

FIG. 3 is a schematic showing prior art and the current invention. Bottom) the prior art
30   shows molecules attracted to coatings through weak intermolecular forces. Top) the current

invention shows bonding of an analyte to the coating. Here the analyte may be localized at the coating through an intramolecular force (e.g. a chemical bond) that strongly holds onto the analyte.

5   FIG. 4 is a schematic representation of how the detection system may work on a molecular basis, and includes a depiction of a sensor molecule (and some subunits), its attachment to a surface, and its subsequent reaction with an analyte.

        FIG. 5 shows some abbreviated chemical structures illustrating the types of acyl carbon derivatives which could be used as the RFG portion of a sensor molecule.

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        V.   BEST MODE OF CARRYING OUT THE INVENTION

        As can be easily understood, the basic concepts of the present invention may be embodied in a variety of ways. It involves both analysis techniques as well as devices to
15   accomplish the appropriate analysis. In this application, the analysis techniques are disclosed as well as various devices described and as steps which are inherent to utilization. In addition, while some devices are disclosed, it should be understood that these not only accomplish certain methods but also can be varied in a number of ways. Importantly, as to all of the foregoing, all of these facets should be understood to be encompassed by this
20   disclosure.

        The general spectroscopic technique can be easily understood from reference to Figure 2. Figure 2 shows an analyzer (1) which has some type of input (2) and results in some type of output (3). Either by providing the analyte or controlled substance itself or by providing an
25   input where some type of sample surface or sample (4) can be provided to the analyzer (1), input (2) facilitates sample (4) to be provided within analyzer (1). Since the focus is upon analysis through spectroscopy, analyzer (1) as well as the various components are configured for spectroscopic analysis. Either within or external to analyzer (1), some type of source (5) may provide one or more wavelengths of energy to which a spectroscopic
30   sample (4) is exposed. The source (5) may be a laser or some other type of highly regulated

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light source. It may also be some type of broad spectrum source. Typically, the source (5)

has been highly regulated to provide a constant output. In keeping with one of the aspects

of the present invention, less expensive sources might now be used. In general, however,

the spectroscopic sample (4) may be provided so that the source (5) can be exposed to it in a

manner that at least one incident wavelength of energy can impinge upon the sample (4). In

5 this way source (5) -- which may be virtually any type of illumination device -- can

illuminate the sample (4). Since most spectroscopic analysis which is of interest in the

present invention involves the analyte being on some type of surface, sample (4) may

configured as a spectroscopic sample surface. As such the sample has the appropriate

characteristics for a particular spectroscopic technique. In the situation of Surface Enhanced

10 Raman Scattering, the spectroscopic sample surface may have such characteristics as those

skilled in the chemical arts readily understand so that the spectroscopic sample surface can

interact and provide an appropriate Raman scattering or surface enhanced Raman scattering

as the case may be. The spectroscopic sample surface may include on it some type of event

location which may either be the entire surface or singular locations (such as wells) so that

15 many different analytes or sensors can be utilized.

In keeping with the present invention, the spectroscopic sample surface may be adapted

so as to retain the analyte through some type of attachment link. While in the prior art, this

attachment link may have include primarily weak interactions, in the present invention a

20 significant difference may be provided so that the attachment link creates either a permanent

link or perhaps a covalent link in some manner. Regardless of the specific type of link, the

attachment link is designed so that at least at one spectroscopic sample location the analyte

or controlled substance can be linked in some manner which can be spectroscopically

sensed, that is, in a manner so that an appropriate spectral change exists as a result of the

25 analyte's presence. A significant departure by the present invention with respect to the

teachings of the prior art is that this link may retain the analyte -- or at least some

component chemical or other aspect of the analyte -- through formation of a covalent bond,

or stronger interaction.

30   When the source (5) provides at least one wavelength of energy, the incident wavelength

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of energy can be affected in some manner at least in part by the analyte as it is retained on the spectroscopic sample surface. This broad possibility, namely, the fact that it merely affects the spectroscopic signal means that the signal can either be a totally new signal (such as that of an adduct), or it can simply alter the signal in some indirect manner by the presence of the analyte. The alteration then results in a spectroscopic signal which is

5   typically changed emission or adsorption wavelength(s) of energy so as to produce a signature which can be analyzed and determined uniquely as a result of the presence of the particular analyte desired. The sample (4) can either have on it, or be itself, some type of sensor molecule which interacts with the analyte. The changed wavelength or wavelengths may then be further focused or conditioned by optics (6) so that some type of detector (7)

10 can be positioned to receive the changed wavelength or perhaps the spectroscopic signal. This signal can then be provided for some type of analysis.

   The analysis may consist of a computer determination through comparison software or some other determination, all as is well known, to gain information with respect to the

15 analyte or controlled substance. Thus, the analyzer (1) acts so as to spectroscopically analyze the signal. This analysis may be as simple as comparisons to known spectra or other data which may be stored in a computer or other such device.

   As mentioned, it may be desirable to have a spectroscopic sample surface. As those

20 skilled in the chemical arts readily understand, for Raman spectroscopy this spectroscopic sample surface may actually be a Raman spectroscopic sample surface or a Raman surface, namely, a type of surface which provides the appropriate interactions to achieve the Raman scattering phenom- enon. Similarly, for Surface Enhanced Raman Scattering spectroscopy this spectroscopic sample surface may actually be a Surface Enhanced Raman Scattering

25 spectroscopic sample surface, namely, a type of surface which provides the appropriate interactions to achieve the Surface Enhanced Raman Scattering phenomenon. Likewise, the illumination source may be a specific Raman illumination source, namely, the type of source appropriate for Raman Spectroscopy so that Raman illumination is exposed to the sample (4) to produce Raman scattering or a Surface Enhanced Raman Scattering

30 illumination source. It should also be understood that the surface, while typically a

somewhat planar solid, may also include suspended particulates and the like so long as an

appropriate Raman or other sensor molecule type is included to permit the interactions

desired.

As mentioned earlier, the focus on spectroscopic analysis differentiates the invention

5 from other separation types of techniques. Such techniques may include chromatography or

other aspects which, although often incidentally used, are fundamentally different from the

field of spectroscopic analysis. Chromatographic techniques often simply separate materials

on the basis of their interaction with a surface. Here, early chromatography used paper,

activated charcoal, or alumina to separate polar materials from a nonpolar solvent phase.

10 This allowed the analytical chemist to remove polar interference from a nonpolar analyte or

to sequester a polar analyte onto a stationary matrix and flush away nonpolar interferences.

As the chromatographic field has advanced, it is possible to separate materials based on

smaller and smaller differences in affinity for the solid stationary phase. More recently, the

field of liquid chromatography has improved through the use of affinity coatings. The

15 coatings allow one to chemically modify the solid stationary phase such that it possess

affinities different from the uncoated material. A classical example is the coating of silica

which is a very polar surface with an alkylsilane to produce a very nonpolar surface. This

makes it possible to partition nonpolar materials onto the stationary phase and to have a

polar solvent phase (mobile phase). This form of chromatography is called reverse phase

20 chromatography. The realization that coatings could be used to modify the chemical

properties of the solid phase led to the development of charged coatings. These are used for

yet another form of chromatography called ion chromatography. This form of

chromatography utilizes Coulombic attraction and polarization forces to separate charged

species from a noncharged mobile phase. All of the above described chromatographic

25 methods use an interfacial forces for separation. While they may be incidentally used in the

preparation of samples for spectroscopic methods, they are not themselves a spectroscopic

analysis technique. Similarly, affinity chromatography which is often used to isolate or

purify enzymes, may involve transient bonding to substrates, however, again, this technique

is primarily a separation technique and is not designed for spectroscopic analysis. The

30 transient bonding is of necessity nonpermanent as it is simply an intermediate step of

enzyme activity and is designed to be released.

Although the prior discussion with regards to spectroscopic techniques focused upon the utilization of SERS and Raman technology, it should be understood that a variety of detections systems could be employed with the present invention to determine the

5 concentration or characteristics of the analyte. At present it simply appears that the most attractive is Surface Enhanced Raman Spectroscopy (SERS) because of the tremendous increase in Raman signal intensity associated with localizing a molecule near a silver, copper, or other appropriate metal surface. SERS is also attractive due to the high information content associated with Raman spectroscopy, which assays the transitions

10 between vibrational states of a molecule. Infrared (IR) spectroscopy, which also detects vibrational transitions in molecules, is also a good candidate for a detection system. Because the sensor coating and subsequent adduct coating are both surface bound, the most probable application of IR spectroscopy would be in the context of direct-, or indirect-reflectance Fourier transform infrared spectroscopy (FTIR), in which the lower sensitivity of

15 the technique could be compensated by the multiple acquisition and subsequent analysis of spectra. Other optical techniques which might be applied to measuring concentrations of the surface bound species are fluorescence (or phosphorescence) spectroscopy, or the measurement of fluorescence (or phosphorescence) lifetimes. Non-optical techniques which could be utilized for these measurements could include electrochemical methods (e.g.,

20 voltametric or amperometric methods). In the simplest cases (e.g., those in which only a single analyte is likely to be encountered), any other method (spectroscopic or nonspectroscopic) which can be used to characterize the presence of a species at a surface could also be utilized, provided that it could distinguish between the sensor coating and the adduct coating. More demanding applications (i.e., more than one possible analyte) would

25 probably require a technique which could distinguish between the sensor coating and each of the possible adduct coatings.

As disclosed, the coating may consist of a variety chemical classes. Carbon containing groups such as those having some carbon atom in their structure and even non-protein

30 groups of coatings could be used as the reactive coating. As contemplated in one of the

17

preferred embodiments, a diazonium compound or some derivative of that compound could be used as a sensor coating. The diazonium compound may also include a diazonium salt sensor coating. Any diazonium compound sensor coating could be selected in situations in which the particular analytes involved would react appropriately with the diazonium compound sensor coating in order to provide the desired spectrum. Thus, a controlled

5 substance which reacted appropriately would be considered a diazonium-specific controlled substance. In this manner at least some chemical of the diazonium-specific controlled substance would interact with the analyte-reactive coating (8). Some chemicals which represent both controlled substances and appear to be appropriate as a diazonium-specific controlled substance include codeine, heroin, psylocibin, tetrahydrocannabinol and

10 morphine.

Some other specific coatings in keeping with this aspect of the present invention may include activated acyl compounds and their associated acyl-specific controlled substances or analytes. The substances may include not only those mentioned earlier, but also some

15 alcohols, amphetamines, or methamphetamines. Nitroso-sensor coatings may also be used with nitroso-specific analytes as is mentioned later.

As discussed in more detail later, any of the coatings may be placed on the desired surface through techniques easily understood and may thus be used to sense the appropriate

20 substance. This substance may range from general analytes to the controlled substance application mentioned earlier to medical applications as well. In that latter instance, blood substances, namely, those being blood itself or coming from or derived from blood products may be used for detection of either controlled substances or medically important information such as bilirubin or the like. In an analysis, even finger printed or complex

25 spectral characteristics could be provided or used within computer or other capabilities so that individualized determinations might be made. Other applications beyond those mentioned range from mining to environmental applications. Naturally many of these substances would beconsidered controlled substances -- that is, they are regulated in some way, be it due to illegal drug use, environmental concerns, or for other reasons.

30

As mentioned earlier, the linking between the analyte and the coating on the surface of the sample (4), may be selected so as to achieve not merely permanent bonding of the coating to the surface, but, significantly, permanent bonding of the analyte to the coating. Unlike the weak interactions considered appropriate in the prior art, this latter permanent bonding can include links which are merely retained to a significant degree, links which

5   might be truly nonremovable in ordinary use, or even some type of intermediate level of linking. The bonding may include, of course, a covalent bonding such as those skilled in the chemical arts readily understand to be highly permanent or such as may even create a new molecular species. Such a species, namely, the combination of the analyte or controlled substance and the coating can be an adduct or even a covalently bonded adduct. In this

10 embodiment even if a new species (or more importantly spectral signature) is created, the invention recognizes that the original spectral characteristics of the analyte need not be necessarily retained, but rather the spectral characteristics of the adduct may be adequate. Thus an adduct of any kind whether permanent or not, may to some degree present a significant difference over the prior art. Thus, by selecting a coating which is adapted to

15 form a covalent bond with a particular analyte, the original signature of the analyte may be lost, however, the new signature -- that of the covalently bonded adduct might now be present. In creating an adduct the spectroscopic signal present may now be very different and may not even be an analyte signal but rather an adduct-specific signal which is produced by the treated surface.

20

A coating as described above may be specifically created through the use of some sort of reactive functional group which would itself be adapted to form the desired adduct. As is mentioned later, an interesting aspect is that through this technique even slight variations in the reactive functional group of the coating can give very different spectral signals. For

25 instance, simply relocating the functional group on a scaffolding or creating different types of bonds can be used to alter the spectral characteristics and yield a very different spectrum for different analytes or different circumstances.

By including the possibility of creating an adduct as opposed to weakly linking the

30 analyte to the surface, a situation where the equilibrium constant for locating the analyte or

adduct at the surface is essentially at infinity can be created.

As mentioned earlier, one of the advantages of utilizing permanent or perhaps covalent bonding of the analyte or controlled substance to the spectroscopic sample surface (4) is that once these bonds have been created, they may not be easily removed or broken. Thus it may

5 now be possible for some analytes to wash the surface with a liquid either to remove excess analyte, to stop the continued creation of the bonding of the analyte over a period of time, or to remove interfering substances. With respect to stopping the creation of additional bonding, a greater degree of accuracy may now be possible in that the sample surface prior to being presented to the analyzer (1) may be washed at a specific time to completely stop

10 any continued creation of the covalent bond. This might also have the added benefit (or independent benefit) of simultaneously removing any interfering substances which can be washed away. Similarly, it is now possible to utilize this washing technique to remove any excess analyte. Again, this may or may not occur simultaneously or may occur independently from the steps of stopping the creation of the covalent bonding of the analyte

15 to the coating or the step of removing interfering substances.

In yet another embodiment of the present invention, the coating may be designed to present an internal standard. By internal standard it is meant that the coating would separately present an unaltered signal which could be sensed to yield information regarding

20 the real time status of the source (5) so that variation in the illumination or detection functions could be factored into the analysis and compensated for without a need for a more expensive laser or other illumination source (5). This internal standard could be a lower or even separate portion of the coating itself. It could also be from a tether group. As such it could present an internal standard which was co-located with the adduct or co-located with

25 the chemical reaction event location (9) so that a singular illumination process could achieve the signal of both a spectrum of the adduct as well as a spectrum for the internal standard. Examples of such an internal standard could include a carbon chain structure, aromatic ring,, non-reactive chromophore, a nitro group, a sulfonyl, a non-carbon structures, or other such items as those skilled in the chemical arts would readily recognize. Such an internal

30 standard could be specifically included in the design of the coating itself.

The construction of the analyte-reactive coating (8) may be achieved in a variety of ways depending on the specifics of the application. One type of design is illustrated diagrammatically in Figure 4. As shown, a sensor molecule possessing a tether (TETH) could be terminated by a surface attachment group (SAG), a reactive functional group (RFG) and possibily even one or more modifier group(s) (Z). These could be placed on a suitable

5   surface to give the sensor coating. In one of the other embodiments, a precursor molecule having a tether, perhaps a modifier(s) Z, and a RFG-precursor (RFG') may be used to coat a suitable surface. By including a precursor arrangement, the coating might be designed so that in a subsequent step, the RFG' could be transformed to the RFG to yield a fully reactive sensor coating.

10

In use, the sensor coating could be exposed to the analyte (A). This analyte may be contained within a solid, liquid or gas under conditions which might allow a chemical reaction to take place between the sensor molecules and the analyte. After an optional rinse of the new adduct coating to remove possibly interfering substances or interfering analytes

15   (IA) which do not react, the adduct coating could then be assayed by an appropriate spectroscopic technique to quantify the amount of adduct and/or remaining sensor coating present. Aspects of each of these steps are discussed in detail below.

As discussed above, the sensor molecule may incorporate a tether, a reactive functional

20   group (or its precursor), and in some instances, a modifier group. All of these groups may be attached to a central molecular scaffolding (CMS).

Since the surface attachment group is designed to hold the coating to the surface, the choice of SAG would likely depends on the surface involved, as well as on the functionality

25   present in the sensor molecule (see below for a discussion of the latter issue). In each instance the surface attachment group, namely, the portion of the molecule which would serve to link atoms in the sensor molecule to the surface could be chosen based upon the type of substrate or surface which is desired to be used. The following discusses a variety of such surface materials; naturally others could be used and in such instances, the SAG would

30   likely be varied as those skilled in the chemical arts would readily understand.

Metal surfaces. Likely metal surfaces include silver, gold, copper and mercury. A particularly appropriate SAG for these surfaces appears to be the thiol group RSH (or RS-) or some derivative of the thiol group such as $RCOSM$, $RCOS_2M$, $ROCOSM$, $RSCOSM$, $RSCS_2M$, $ROP(S)_m(O)_{3-m}M_2$, $RSP(S)_m(O)_{3-m}M_2$, $RSSR'$, $RSSSR'$, $RSNR'R''$, in which R = RFG-Ar-spacer-, M = H or metal ion, and R', R'' = alkyl or aryl or H. Other SAG's which

5 might be appropriate are the polar groups RSO_3M, RSO_2M, $ROSO_3M$, $ROSO_2M$, RCO_2M, $ROCO_2M$, $RNR'CO_2M$, $ROP(O)O_2M_2$, $RP(O)O_2M_2$.

Silica, alumina, or florasil surfaces. In addition to the polar groups listed for metal surfaces above, polar SAG's likely appropriate for attachment to these surfaces include

10 $RR'R''N$, $RR'R''R'''N+$, and the corresponding phosphine and phosphonium salts in which P replaces N. Other SAG's include $RSiX_3$ (X = leaving group such as halide, inorganic ester, and R, R', R'', M defined as for the metal surfaces above), and $RSi(OR')_3$.

Ion exchange resins. Any of the negatively charged SAG's listed under the metal

15 surfaces section above (i.e., $RCOSM$, $RCOS_2M$, $ROCOSM$, $RSCOSM$, $RSCS_2M$, $ROP(S)_m(O)_{3-m}M_2$, $RSP(S)_m(O)_3-mM2$, RSO_3M, RSO_2M, $ROSO_3M$, $ROSO_2M$, RCO_2M, $ROCO_2M$, $RNR'CO_2M$, $ROP(O)O_2M_2$, $RP(O)O_2M_2$) could be loaded onto an anion exchange resin. Amine, ammonium, or phosphonium salts could be loaded onto cation exchange resins. While coatings of this type would be particularly appropriate for use with

20 analyte solutions not containing potentially competing ions, it may still be possible to utilize these systems for ion containing solutions, since many of the SAG's listed above have particularly high affinity for ion exchange resins, and because appropriate tether design could hinder the exchange rate with undesirable ions.

25 Plastics. Any of a number of functionalized polymers could be modified with an appropriate SAG. For example, chloromethylation of a polystyrene based plastic could be followed by reaction with RSM, ROM, or RNR'R''. Alkyl acrylate or alkylmethacrylate polymers could be subjected to ester exchange with ROH, or aminolysis with RNR'H. It may also be possible to adhere a hydrophobic tether group to a hydrophobic plastic through

30 simple hydrophobic attraction.

Cellulose. An example of this class of surfaces is filter paper. This could be modified by any type of activated carbonyl compound (e.g. RCOX, RNCO, R and X defined as in the metals and silica sections above). Modification of specialized cellulosic material (e.g., cyclodextrins) offers the possibility of unique selectivities towards certain analyte classes.

5   Coating Methods. There a number of possibilities to create the coating. While many of these are easily understood by those of ordinary skill in the chemical arts, two general approaches may be noteworthy in the formation of a sensor coating: application of RFG-Ar-tether-SAG to give the sensor coating directly, or application of RFG'-Ar-tether-SAG, in which RFG' is a group which must be transformed to the desired
10 RFG in a subsequent activation step. The advantages of the first approach are at least two-fold. The prior activation/formation of the RFG should be straightforward, since the reactions leading to it should generally be standard solution phase chemistry. In addition, this approach should typically yield the sensor coating directly. There are, however, potential disadvantages of this approach for some classes of sensor coatings and/or SAG's.
15 These disadvantages include the possibility that the sensor coating may not have a long term stability (e.g., due to reaction with adventitious water, oxygen, light), and the possibility that a particular combination of RFG and SAG may not be chemically compatible, or that the RFG may not be compatible with the surface during the coating process (due to the geometry of attachment of the sensor molecule and tether, it could be possible that one
20 could have RFG's which could react with a surface in the process of coating, but could not react once attached to the surface). While it is likely that the potential problem of sensor coating stability could be solved simply by appropriate protective measures (e.g., a dissolvable overcoating, or the use of otherwise hermetically sealed surfaces), the problem of SAG/RFG incompatibility may require the second approach, in which the RFG is formed
25 only after surface coating. In addition to avoiding the problem of functional group incompatibility, this approach may be desirable from the standpoint of sensor coating stability. In practice, a stable pre-sensor coating could be prepared, stored for some indefinite period of time, and then the RFG' converted to the RFG by activation immediately prior to exposure to the analyte. A potential drawback to this approach is the possibility that
30 the desired RFG activation might not occur efficiently on a surface. In some cases, the

feasibility of this approach might even need to be determined on a case by case basis. Other

approaches may be appropriate depending on market place and other considerations and

should be relatively easily designed once the basic principles are understood.

Again, it should be understood that each of the above examples represent merely some

5   choices available depending upon the particular surfaces or other aspects involved in a

particular application. Variations should be understood as encompassed within this

disclosure since with the basic teachings those of ordinary skill in the chemical arts would

be able to achieve variations in any of the components mentioned without undo

experimentation.

10

Attached either directly to the surface attachment group or through some type of tether,

may be a central molecular scaffolding. The Central Molecular Scaffolding may serve to

physically hold the various components of the sensor molecule in place. It may also play a

role in the analysis of the adduct coating. This could be particularly true in the case of

15   spectroscopic techniques which rely on fluorescence, or which require detection at long

wavelengths, for which polycyclic aromatic scaffoldings might be particularly well suited.

If the modifier Z is to have a direct influence on the reactivity of the RFG, or upon the

spectroscopic characteristics of the adduct coating, it might preferrably be desirable to have

a direct electronic "connection" between Z and the scaffolding, and between the scaffolding

20   and the RFG (and subsequently the analyte portion of the adduct). Once again, this might

suggest a central scaffolding which might likely be a monocyclic or polycyclic aromatic (or

heteroaromatic) ring. For sensor coatings which primarily act by ensuring the propinquity

of a target analyte to the surface, it may not be useful to have the electronic connection

discussed above. For these systems it may be possible (though not necessary) to employ

25   non-aromatic scaffoldings. In general, however, examples of some central molecular

scaffolding groups may include similar types of rings as mentioned earlier with regard to the

surface attachment group, namely, the establishment of the monocyclic aromatic ring, a

polycyclic aromatic ring, a heteroaromatic ring, or a non-aromatic scaffolding as well.

30   As mentioned earlier, one of the advantages of an embodiment of this invention is the

possibility of removing undesired substances which might have spectral characteristics which interfere with analysis of the target analyte. This may be accomplished by washing the surface layer subsequent to reaction, thus removing the unreacted, interfering substances. From the above description, it may be gathered that this general approach to analyte specificity and enhanced signal-to-noise is not expected to be limited to a specific

5   type of surface, though certain of the spectroscopic methods used for final analysis may require specialized substrates (e.g., silver, gold or copper for use with SERS).

As previously discussed, the surface attachment group may be linked to the central molecular scaffolding through some type of tether. The tethering group attached to the

10 sensor molecule may simply be zero to many carbon or non-carbon atoms in a chain (or incorporating a ring) terminated by a SAG which is appropriate for attachment to the chosen surface. Alternatively, the tether may incorporate a nonreacting chromophore of some sort (e.g., some type of aromatic ring). Such incorporation could allow for the possibility of using the tether chromophore as an internal standard for quantification of the spectroscopic

15 changes on going from the sensor coating to the sensor adduct coating. Tethering chains incorporating aromatic or long-chain aliphatic carbon chains (or perfluorinated carbon chains) also may prove to be advantageous from the standpoint of stability of the sensor coating, since the hydrophobicity of these groups could tend to protect the surface attachment points from the solvent and dissolved solutes. In the case of detection systems

20 designed for use with nonpolar solvents (e.g., one of the activated acyl based sensor molecules), a polar, nonreacting tether could be utilized. Examples of this type of tether would likely be amide based (e.g., a polypeptide, possibly terminated with cysteine), though other polar tethers could also be employed (e.g., based on sulfonates or sulfoxides). A tether design which would be especially effective in masking a surface from an organic

25 solvent would be one of the type $RFG\text{-}Ar\text{-}(CH_2)_n\text{-}N^+R_2(CH_2)_m\text{-}SAG\ Y\text{-}$ ($Y\text{-}$ = counterion), since the ionic interface could effectively preclude migration of nonpolar molecules.

Functionally, an important aspect of the coating may be the inclusion of some type of reactive functional group, namely, a group of atoms which acts in such a fashion as to react

30 with the analyte and link the analyte to the coating. The coating itself may thus be adapted

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to be attached to the analyte of desire. This attachment may occur through a covalent bond, the mere creation of an adduct, some type of permanent link, or otherwise. Because of the importance of this structural feature of the sensor molecule, and because of the differences in analyte specificity which result from differences in the nature of the RFG, its location and the like, the various classes of RFG's are discussed with some specificity below. General

5 examples of reactive functional groups which can be used include not only the diazonium groups, azo species, and nitrosos, but also activated acyl sensors as well as non-protein molecules.

Diazonium. The diazonium group is probably the most interesting and promising of the

10 RFG's due to its high reactivity towards certain classes of molecules, as well as the nature of the adduct it can form with these molecules. While the high reactivity of diazonium salts is well known, and is responsible for their utility in the preparation of diverse functional derivatives of aromatic rings, these ions are not indiscriminately reactive. Thus, proper choice of reaction conditions for their formation leads to diazonium salts which can be kept

15 for long periods in solutions and subsequently reacted with an added reagent, or even isolated and stored for long periods of time prior to redissolution and reaction. One of the characteristic reactions of diazonium salts is the addition of a nucleophile (Nuc) to the terminal nitrogen of the ArN_2+ group to give azo species Ar-N=N-Nuc. As a consequence of the high degree of conjugation and polarizability of these azo species, they are in many

20 cases dyes, and appear especially well suited by virtue of wavelength of maximum absorption (λmax) and/or extinction coefficient (ϵ) to detection by any of a number of techniques. Alternative pathways for nucleophiles involve substitution (directly, or indirectly through the intermediacy of an azo species) of the N2+ group to give a new aromatic species. Though the new species often may not have as desirable spectral

25 characteristics as the azo type products, the replacement of the unique N2+ chromophore by a different group typically is distinct. One of the classical reactions of diazonium salts, that can result in the formation of aryl chlorides and aryl bromides, follows a radical pathway demanding the presence of copper (or other metal) salts, and may be unlikely to occur except under specially designed conditions.

30

26

Nitroso. Aryl nitroso compounds are expected to share many of the same desirable features of diazonium salts in terms of their reactivity with selected classes of potential analytes, and in terms of the desirable spectral characteristics of the resulting adducts. Aryl nitroso compounds may react with amines to form azo compounds (Z-Ar-NO + RNH2 gives Z-Ar-N=N-R) which, as indicated above, sometimes form the basis of many dyestuffs.

5 If an electron rich phenol or aromatic amine is employed, then nitroso compounds may react to form quinoimine, or quinodiimine type structures. These reactions can be exemplified by the formation of the dye gallocyanine (from gallic acid and p-nitrosodimethylaniline) and Nile Blue A from 1-naphthylamine.

10   Activated Acyl Sensors. This class of RFG or sensor molecules comprise compounds having a reactive acyl type carbon. In addition to compounds in which the reactive carbon is in the oxidation state of a carboxylic acid (e.g., acid chlorides, imino esters, iminium esters, etc.), this class of compounds should be understood to include compounds in which the reactive carbon is in the oxidation state of carbon dioxide (e.g., carbonyl halides

15 (ROCOX), isocyanates, diimides, etc.). Examples are illustrated in Figure 5, along with the structures of the adducts expected upon reaction with alcohols and amines (RXH, X = O and NH or NR', respectively). All of these compounds are expected to be highly reactive towards water, and thus it is likely that sensors based on this type of reactive functional group will be of greatest utility for directly assaying non-aqueous and non-alcoholic

20 solutions. Exceptions to this generalization may, of course, occur if the analyte of interest is of sufficiently great reactivity (and sufficiently high concentration) that it may compete with water/alcohol for the RFG. An alternative to directly assaying an aqueous sample might involve extraction of the analytes of interest from an aqueous solution into an organic solvent, followed by exposure of the extract to the sensor coating. Similar considerations as

25 those discussed above for the preparation of the sensor coating may apply here as well. Although direct formation of a surface from a molecule incorporating the desired RFG may have some practical benefits, depending on the specific identities of the RFG and SAG, it may be necessary or advantageous to prepare a coating having from a molecule which has a group RFG' that may be unreactive, but which may be transformed to the RFG after

30 formation of the coated surface.

Both the diazonium and activated acyl sensor coatings might be used for the detection of
controlled substances and the like. Particularly the activated acyls may also be used for
alcohols and amines as well. The nitroso coatings though likely not as applicable for drug
sensing also may offer specific chemicals for which they are appropriate. In general, the
sensor coatings may include a wide variety of general type and classes of molecules such as

5   those including a halide, an electron-donating group, an alkoxy group, amide group, amino
group, an electron-withdrawing group, a nitro group, a carboxlic acid group, an ester group,
a sulfoxide group, or a sulfone group, diazonium salts, electrophilic carbons, or a carbonyl
group.

10   The large variations in reactivity of aromatic compounds with aryl diazonium salts may
allow a significant degree of selectivity to be achieved in the analysis of mixtures of
compounds. In a gross sense, aromatic analytes may be divided into electron rich and
electron poor groups. Aromatic compounds more electron poor than benzene are not
expected to react with Z-Ar-N2+, though exceptions may be possible. Electron rich analytes

15   susceptible to analysis through diazonium based surface coatings include phenols, diaryl
ethers, aryl alkyl ethers, aryl esters, aryl amines (anilines), aryl amides (ArNRCOR'),
pyrroles, furans, thiophenes, and any other electron rich heteroaromatic ring system. For all
of these compounds, the direct conjugation of the two aromatic rings through the diazo
group may mean that adducts could have very unique and distinguishable spectral

20   signatures.

To further permit variation in the reactive functional groups and the analytes for
controlled substances desired to be sensed, it is possible that the reactive functional group
may be first presented as a reactive functional group precursor. In this fashion the group

25   itself would not act at its initial configuration to achieve the reaction with the analyte but
rather would require some type of activation step to convert it to its reactive form. Such
may be presented by subjecting the reactive functional group precursor to an activation
substance. In this manner the reactive functional group precursor might be activated to
produce a reactive functional group, namely, a substance which in its activated state would

30   act to react with a desired analyte. Thus, the reactive functional group precursor might be

activated to become the chemical reaction event location by being subjected to some type of activation substance. Examples of reactive functional group precursors include: but are not limited to aryl amines (for diazonium RFGs), aryl amines or hydroxylamines or nitro groups (for nitroso RFGs), and carboxylic acids or alcohols or amines (for activated acyl group RFGs). Examples of activation substances include: sodium nitrite, thionyl chloride, and the

5   like as those skilled in the chemical arts would readily understand.

To permit even further variation, for certain classes of substrates, it may be possible to modify reactivity (and thus, selectivity in a sample containing mixed analyte classes) in either a positive or negative sense through manipulation of the reaction conditions. This

10   strategy may be illustrated by considering a mixture of a phenol (ArOH), aryl ether (ArOR, R either aryl or alkyl) and an amine (ArNR2). At pH 7 all of these compounds are expected to be in the neutral forms given above, and the better donor ability of nitrogen as compared to oxygen should result in a reactivity order of ArNR2 > ArOH ≈ ArOR, allowing for selective/enhanced detection of the aryl amine. At higher pH (>8-9), significant ionization

15   of the phenol may generally take place to give phenolate, ArO-. Phenolate ions are among the most reactive species known towards diazonium salts, often showing near diffusion controlled rates of reaction. Thus, at conditions of high pH, the reactivity order is expected to be "ArOH" > ArNR2 > ArOR. Indeed, selectivity of this type has been seen in the case of the reactions of 5-dimethylamino-1-naphthol with benzenediazonium ion. In this case,

20   reaction occurs para to the dimethylamino group at low pH, and ortho to the oxygen at high pH. Finally, if exposure of a sensor coating were to take place at very low pH (e.g., pH ≤3), the amino group of the arylamine would be in a protonated state (ArNR2H+), rendering the aromatic ring highly electron deficient and unreactive. Under these conditions the reactivity order should be ArOH≈ ArOR > "ArNR2", allowing the assay of phenols and aryl ethers in

25   the presence of the normally more reactive aryl amine.

It is possible that attachment of the RFG and tether/SAG units to a central molecular scaffolding may result in a coating which reacts at a desirable rate with target analytes to give adducts having desirable characteristics from the standpoint of subsequent analysis. If

30   these conditions are not met, however, it may be desirable to incorporate a modifier group,

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Z. The modifier (if employed) could be chosen so as to influence the reactivity of the RFG, although it may also play a role in enhancing the spectral characteristics of the adduct coating (e.g., in terms of λmax, extinction coefficient). In order to increase reactivity, it is likely that an electron withdrawing group would be chosen (e.g., nitro, carboxylic acid, ester, sulfoxide, sulfone). The nitro group illustrates the dual role which a modifier could

5   play. In addition to increasing the reactivity of either a diazonium or activated acyl based sensor towards all analyte classes, the nitro group may appear particularly Raman active, suggesting its utility in a SERS based detection system.

Thus, this arrangement could present a first modifier and a second modifier which could

10   be attached to some aspect of the coating to achieve the desired result. In one regard the modifier might serve to reserve a position on the molecule to react with the controlled substance or the analyte involved. In another regard the modifier might serve to influence the reactivity between the reactive functional group and the analyte. This influence might actually serve to tune or influence the reaction to a desired degree. In one regard such

15   tuning might serve to provide different ranges or concentrations at which the analyte reactive coating (8) would react. Thus, the sample (4) might be configured with a variety of sensor locations for each to serve as a sensor appropriate to a different range of concentrations. It should be noted in this regard that in other aspects of the invention multiple sensors can be essentially co-located at one sensor site to potentially achieve a

20   similar type of capability. Regardless, the modifier might serve to create a group which could be adapted to influence the activity between the coating and the analyte to some desired degree. Interestingly, the modifier through its location on the reactive functional group or some other aspect can set different ranges based on the type of modifier chosen. Since these range variations can be many orders of magnitude different, a great degree of

25   variation can be achieved through this embodiment of the present invention.

Examples of modifiers which may be utilized include electron donating groups (oxygen or amine nitrogen or amide nitrogen), electron withdrawing groups (nitro, carboxylic acid, esters, sulfoxide and sulfones). As before, and as should be understood throughout this

30   application, the examples should not be viewed as establishing a limitation to the invention.

30

Under the basic teachings of the present invention those with ordinary skill in the chemical

arts can easily vary the chemicals to achieve the desired result based upon the type of

situation or type of analyte involved. Furthermore, a great degree of variations in the

various substances involved is explained in Figure 5. This teaching serves as a blueprint for

the design of a great variety of chemicals according to the present invention.

5

As mentioned earlier, this invention has applicability in a variety of instances ranging

from law enforcement to medical to environmental concerns. With the teachings of the

present invention one need only understand the particular analyte involved and then utilize

the teachings to attempt to design an appropriate reactive functional group or

10 analyte-reactive coating (8) to achieve detection or analysis.

Without creating a limitation, some of the various analytes naturally include many

controlled substances such as codeine, heroin, possibly cocaine, tetrahydrocannibinol

(THC), morphine, amphetamines, methamphetamines, or the like. They also include a

15 variety of other substances as discussed below. Analytes which should be well suited to

detection by diazonium based sensor molecules include the following classes and types of

substances.

Cyanide. Cyanide can react in a reversible fashion with $Z\text{-}ArN_2+$ to give $Z\text{-}Ar\text{-}N=N\text{-}CN$.

20 It is of note that while this reaction is reversible, it involves the formation of an adduct

which results from covalent bond formation. This complex may be orange or red, depending

on the geometry about the $N=N$ double bond. There are two aspects of this reaction which

may be of practical importance: its reversible nature, and the sensitivity of the reaction to

the nature of Z. The reversible nature of this reaction means that it may be possible to

25 construct a detection system which may be used multiple times (with appropriate

intermediary rinses) and/or as a flow sensor to detect changing concentrations of cyanide in

a waste stream. The sensitivity of the reaction to the nature of Z offers the possibility of

making a detection system which is capable of quantifying cyanide concentration over a

wide range of values. The Hammett equation for this reaction is $\log(K_{CN}) = 3.53\sigma + 1.82$.

30 Thus, the equilibrium constant K_{CN} for the reaction ranges from 60,000 M-1 for Z = p-NO$_2$

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to 15 M^{-1} for Z =p-CH_3. By employing mixtures of sensor molecules (each of which may have a unique spectrum), it may be possible to monitor a wide range of cyanide concentrations, since levels which may saturate (i.e., overload) a sensor molecule having Z = p-NO_2 typically may just be starting to effectively form adducts with a sensor molecule having Z = m-Cl (for which K_{CN} is 1,600 M^{-1}). Since the spectra of differentially substituted

5   adducts may be different, it generally will be possible to distinguish between them and determine their concentrations. It should be noted that since some cyanide bonds -- while covalent -- may not be totally permanent, such adducts may not be appropriate for a washing procedure discussed earlier.

10   Sulphite. The sulfite ion undergoes very rapid reaction with aryl diazonium salts to give the syn isomer of the adduct Z-Ar-N=N-SO_3-. This intermediate may then undergo an isomerization reaction to give the stable anti adduct, or under conditions of high sulfite concentration may add a second sulfite to give the bis-sulfite adduct Z-Ar-N(SO_3-)NHSO$_3$-. The rate of the syn-anti isomerization reaction is substantially slower than that of the initial

15   adduct formation, with half-lives of about 250 sec and <2 sec, respectively. Furthermore, the rate of this isomerization is not greatly dependent on the identity of Z. With this relatively slow isomerization, it may be possible to directly measure sulfite concentrations by spectral assay immediately following exposure of the sensor coating to the analyte sample. However, by simply waiting for roughly 30 minutes (which is seven half-lives for

20   the isomerization reaction), the isomerization reaction may be >99% complete, allowing concentrations to be measured from the spectrum of the anti mono-adduct. A further advantage of this approach may be that the secondary reaction of the syn- or anti-mono-adducts to give the bis-sulfite may provide a method by which higher concentrations of sulfite can be measured. Thus, molecules of this type may inherently be

25   dual-range sensors.

Thiols. It may be possible to detect thiols and related species (e.g., xanthates) through the formation of adducts of the type Z-Ar-N=N-SR. The possible competing process of the binding of the thiol to the surface (for metal substrates) could be minimized by having a

30   high level of surface coating density for the original sensor coating. In any case, should the

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thiol bind to the surface, it might be possible to detect its presence directly by spectroscopic means.

Sulfinic acids. Sulfinic acids react with Z-Ar-N_2+ to give Z-Ar-N=N-SO_2R, and thus should be amenable to detection by a diazonium based sensor coating. The extent of adduct

5 formation, as well as the reversibility of adduct formation appears similar to that found with cyanide. Hence, such potentials for sensor coatings may be similar to those discussed for cyanide (e.g., reusable, applicable to flow systems, wide dynamic range through use of mixed coatings, etc.).

10 Amines. Ammonia and primary amines react with Z-Ar-N_2+ to give triazenes, Z-Ar-N=N-NHR (R = H, alkyl; aryl amines are ultimately expected to lead to C-N coupled products, as discussed below for electron rich aromatic compounds). Alternatively, a use of a sensor coating having an oxidizing counterion (such as Br_3-) may lead to formation of aryl azides Z-Ar-N_3 with ammonia as the analyte. This distinction may allow primary amines to

15 be analyzed in the presence of ammonia by either direct observation and quantification of the final mixed adduct coating (Z-Ar-N=N-NHR and Z-Ar-N_3), or by sequential measurements with two different coatings (one with a non-oxidizing counterion, one with). Other derivatives of amines which react with Z-Ar-N_2+ include hydrazines and hydroxylamine. Both of these types of compounds lead to azides and aryl amines. The fact

20 that the reaction of hydroxylamine can be selectively directed by changes in reaction pH to give azides (low pH) or aryl amines (high pH) offers the possibility of distinguishing between the two classes of compounds.

Azide. The azide ion reacts extremely rapidly with Z-Ar-N_2+ to give Z-Ar-N_3. It thus

25 could be spectroscopically sensed as mentioned above.

Carbon Acids. Compounds of the type RCH_2W, in which W is a strong electron withdrawing group (e.g., carbonyl, nitro, etc.) react with Z-Ar-N_2+ to form highly conjugated adducts of the type Z-Ar-NH-N=CRW. These reactions are known to proceed

30 through the conjugate base of the analyte (i.e., $RWCH-$). Although this might be expected

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to mean that this detection method would be limited to strong carbon acids of the type WCH_2W', it appears that while the lower acidity of monoactivated carbon acids RCH_2W (R = H, alkyl, aryl) does indeed lead to lowered concentrations of the reactive conjugate base, there is a compensatory increase in reactivity of the base. Thus, even the relatively unacidic acetone has been observed to couple with benzenediazonium ions under nearly neutral

5   conditions. For carbon acids having only a single acidic hydrogen, adducts of the form Z-Ar-N=N-CRR'W are expected to form. While these adducts lack a direct conjugative interaction with the sensor molecule, the -CRR'W group may still be attached in the vicinity of the surface, and may be susceptible to assay by certain spectroscopic techniques (e.g., SERS, reflectance FTIR) even if it lacks an appropriate chromophore for other techniques

10   (e.g., fluorescence).

     Electron Rich Aromatic Compounds. This class of compounds may prove to be the best suited class of analytes of all those discussed. The coupling of aromatic compounds Ar'-D (D = electron donating group) to aryl diazonium salts $Z-Ar-N_2+$ to give diazo compounds

15   Z-Ar-N=N-Ar'D has been widely studied in the context of the production of dyes. The diazo adducts produced in these reactions absorb UV-Visible radiation strongly (i.e., have high extinction coefficients, ϵ) and typically have their most intensely absorbing peak at high wavelengths (i.e., they have a λmax at high wavelengths), making them particularly well suited for detection by any of a number of spectroscopic techniques. These

20   spectroscopic properties lend themselves particularly well to manipulation through judicious placement of modifier group(s) Z on $Z-Ar-N_2+$, and by variation of the molecular scaffolding Ar.

     Other analytes in general may include phenolic compounds, furans, pyrroles, aryl amines,

25   alcohols, and the like.

     Yet another embodiment of the invention involves its teachings to create multiple sensors. In this regard coatings may be designed which present at least a first sensor molecule type and a second sensor molecule type. These molecule types would be

30   differentiated in that each type would have its own reaction characteristics or its own

differentiatable spectroscopic signal either with respect to the same analyte or with respect to different analytes. As such the first sensor molecule type could respond to a first type of analyte in one way to yield a first signal, and the second sensor molecule type could respond to a second type of analyte in another way to yield a second signal, etc. Naturally a plurality of molecule types could be utilized. In any such design the various sensor molecule types

5   might be adapted to bond with different types of analytes, or, more generally, to somehow differently interact. They may even be adapted to interact differently with the same analyte and may, of course, each create their own adducts for spectroscopic analysis. These adducts would likely yield differentiatable spectroscopic signals in order to permit spectroscopic analysis to gain information about either one or multiple analytes.

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In multiple sensor arrangements in which different analytes might be sensed, either the resulting adduct signal or the coating itself would likely be designed to yield a signal which would provide differentiating information between at least a first and a second species of analyte. In this fashion, a single sensor could be utilized for multiple analytes

15 simultaneously. It could also be used to provide conditional testing in which the presence of one in conjunction with another might yield some type of conclusion. Similarly, as mentioned earlier with regard to amine type analytes, sequential testing is also possible. Examples of this type of arrangement might include physically creating different sensors such as having one event location with a non-oxidizing counterion and another event

20 location with an oxidizing counterion and the like, or might include separate sensor reaction protocols. Thus in one embodiment, the step of subjecting the analyte reactive coating (8) to an analyte may perhaps be specifically applied to a controlled substance or the like to yield multiple adduct types by creating each sensor molecule type to achieve a different adduct result. The differentiated signals might not only yield information with respect to the

25 mere presence of an analyte, but it also might serve for quantitating the presence of either or all of the various analytes sensed.

In a configuration where the same analyte might be sensed, it might be appropriate to configure the first and second sensor molecule types so that their interaction with the same

30 analytes occurred in different concentration ranges or with some other different

characteristics. In applications where different ranges of concentrations were chosen, an

enlarged range of sensitivity for the sample might be presented for a given analyte. These

different ranges might be separate, such as in instances where discrete occurrences occurred

or might more typically be established with awareness of the various saturation levels

involved for the two different types of sensor molecules. In such an application where the

5   first sensor molecule type had a first saturation level (that is, the level at which the changes

in the signal can no longer be accurately discerned for variations in the analyte concertration

or the like) and the second had a second saturation level which was higher than that of the

first, it might be possible to use the first molecule up until it was near its saturation level and

then to use the second sensor molecule type at a continued, expanded range. Furthermore in

10 instances in which an overlap region for the two sensor types might be present, it might be

possible to provide verification of readings in this area via separate interaction mechanisms

so that one could combine both an enlarged range and a verification of readings. In a more

general sense, it would thus be possible to establish complementary ranges, namely, ranges

(whether overlapping or not) which complimented each other for a given application to

15 achieve a desired result (whether verification, expanded range, or otherwise). The first and

second analytical ranges might not even be adjacent if the particular application called for

such an arrangement. Furthermore, even though two different types of sensors might be

provided on a specific coating it is now possible for these two sensors to provide

capabilities, whether used or not, so that in practice one could sense for the presence of

20 different controlled substances or the like with just one sensor plate.

In summary, some of the embodiments of the invention include a surface coating

comprising highly reactive sensor molecules which chemically react with a given analyte

with the formation of a covalent and/or π-bond to give an adduct with spectroscopic

25 characteristics which are unique to the new adduct. This surface coating may provide the

basis of a detection system which combines high sensitivity with high specificity for the

identification of certain analytes. The surface attachment of the sensor molecules allows

reaction of the target analyte(s) to be followed by a rinse, which may remove nonreactive

compounds which may possess interfering spectroscopic characteristics. This methodology

30 contrasts radically from solution based analyte modification methods, in which non-target

impurities may substantially decrease effective detector signal-to-noise ratios. The formation of a covalent bond (sigma or π) between the sensor molecule and the analyte to give a new, unique molecule (termed the adduct) greatly distinguishes this method from those in which hydrogen bonding, or other weak, or perhaps noncovalent interactions may serve to modify the spectral characteristics of a sensor molecule, or to bind the analyte in a

5   location in which its spectral characteristics may be assayed. In one embodiment, the sensor molecules which comprise the coating may have three components attached to a central molecular scaffold: a "tether" terminated by a surface attachment group "SAG," a reactive functional group "RFG" which is highly reactive towards certain classes of molecules, and possibly one or more modifiers "Z" which may serve to increase or decrease the reactivity of

10 the RFG towards target analytes, or to modify the spectral characteristics of the adduct in terms of either wavelength of maximum response to a given spectroscopic assay, or in terms of intensity of response to that assay. Variations in the nature of the tether may allow attachment to a variety of surfaces possessing desirable physical or spectroscopic characteristics. Variation of the RFG, and possibly the conditions under which the coating

15 is exposed to the analyte containing solution, may allow detection selectivity for certain classes of analytes. Variations in the modifier group Z and the central molecular scaffold may significantly influence the nature and efficacy of the spectroscopic technique which is used to assay the presence of the adduct. Variations in these groups may also influence the reactivity of the sensor molecule.

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The discussion included in this application is intended to serve as a basic description from which a great variety of systems can be fashioned. The reader should be aware that the specific discussion does not explicitly describe all embodiments possible; many alternatives are available through application of the teachings of this invention. It also may not fully

25 explain the generic nature of the invention and may not explicitly show how each feature or element can actually be representative of a broader function or of a great variety of alternative or equivalent elements. Again, these are implicitly included in this patent disclosure. Neither the description, the examples, nor the terminology should be taken as an intention to limit the scope of this patent. Since a variety of changes may be made without

30 departing from the essence of the invention, it should be understood that such changes are

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implicitly included within the scope of this invention.

In addition, each of the various elements of the invention and claims may also be achieved in a variety of manners. This disclosure should be understood to encompass each such variation, be it a variation of an embodiment of any apparatus embodiment, a method

5 or process embodiment, or even merely a variation of any element of these. Particularly, it should be understood that as the disclosure relates to elements of the invention, the words for each element may be expressed by equivalent apparatus terms or method terms -- even if only the function or result is the same. Such equivalent, broader, or even more generic terms should be considered to be encompassed in the description of each element or action.

10 Such terms can be substituted where desired to make explicit the implicitly broad coverage to which this invention is entitled. As but one example, it should be understood that all actions may be expressed as a means for taking that action or as an element which causes that action. Similarly, each physical element disclosed should be understood to encompass a disclosure of the action which that physical element facilitates. Regarding this last aspect,

15 the disclosure of a "detection system" or "detector" should be understood to encompass disclosure of the act of "detecting" -- whether explicitly discussed or not -- and, conversely, were there only disclosure of the act of "detecting", such a disclosure should be understood to encompass disclosure of a "detector" or "detection system" (as the context may be appropriate). Similarly, surface "attachment" could include an "attachment element" or

20 "attaching" and vice versa. Such changes and alternative terms are to be understood to be explicitly included in the description.

While the invention explains how to apply knowledge from the skills of persons in different disciplines, to facilitate this and to facilitate the creation of the many variations

25 possible, a list of references is provided in an information disclosure filed with the application. All these are hereby incorporated by reference should they be needed. In any of these references, it should be understood that to the extent statements in any of the references might be considered inconsistent with the patenting of this invention such statements are expressly not to be considered as made by the applicant(s).

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VI.   CLAIMS

We claim:

1   A method for detection of a controlled substance, comprising the steps of:

a.   establishing a spectroscopic sample surface;

b.   placing a diazonium compound sensor coating on said spectroscopic sample surface;

c.   subjecting said spectroscopic sample surface to at least some diazonium-specific controlled substance;

d.   linking a chemical of said diazonium-specific controlled substance to said diazonium compound sensor coating on said spectroscopic sample surface;

e.   exposing said diazonium compound sensor coating on said spectroscopic sample surface to at least one incident wavelength of energy;

f.   affecting said at least one incident wavelength of energy at least in part by said chemical of said diazonium-specific controlled substance as said chemical is linked to said diazonium compound sensor coating on said spectroscopic sample surface to result in a change in intensity of at least one wavelength of energy; and

g.   detecting a spectroscopic signal including said change in intensity of said at least one wavelength of energy;

h.   spectroscopically analyzing said spectroscopic signal to gain information about said diazonium-specific controlled substance.

2   A method for detection of a controlled substance as described in claim 1 wherein said step of subjecting said spectroscopic sample surface to said diazonium-specific controlled substance comprises the step of forming an adduct between said diazonium-specific controlled substance and said diazonium compound sensor coating.

3   A method for detection of a controlled substance as described in claim 2 wherein
said step of forming an adduct between said diazonium-specific controlled substance
and said diazonium compound sensor coating comprises the step of forming a
covalent bond between said chemical of said diazonium-specific controlled
substance and said diazonium compound sensor coating

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4   A method for detection of a controlled substance as described in claim 3 wherein
said step of subjecting said spectroscopic sample surface to at least some diazonium-
specific controlled substance comprises the step of subjecting said spectroscopic
sample surface to a codeine, heroin, psylocibin, tetrahydrocannibinol or morphine.

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5   A method for detection of a controlled substance, comprising the steps of:

a.   establishing a spectroscopic sample surface;

b.   placing an activated acyl compound sensor coating on said spectroscopic

15   sample surface;

c.   subjecting said spectroscopic sample surface to at least some acyl-specific
controlled substance;

d.   linking a chemical of said acyl-specific controlled substance to said activated
acyl compound sensor coating on said spectroscopic sample surface;

20   e.   exposing said activated acyl compound sensor coating on said spectroscopic
sample surface to at least one incident wavelength of energy;

f.   affecting said at least one incident wavelength of energy at least in part by
said chemical of said acyl-specific controlled substance as said chemical is
linked to said activated acyl compound sensor coating on said spectroscopic

25   sample surface to result in a change in intensity of at least one wavelength of
energy; and

g.   detecting a spectroscopic signal including said change in intensity of said at
least one wavelength of energy;

h.   spectroscopically analyzing said spectroscopic signal to gain information

30   about said acyl-specific controlled substance.

6   A method for detection of a controlled substance as described in claim 5
           wherein said step of subjecting said spectroscopic drug sample surface to a
           drug sample which comprises at least one type of acyl-specific drug
           comprises the step of forming an adduct between said acyl-specific drug and
           said activated acyl sensor coating.

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7   A method for detection of a controlled substance as described in claim 6
           wherein said step of forming an adduct between said acyl-specific drug and
           said activated acyl sensor coating comprises the step of forming a covalent
           bond between said acyl-specific drug and said activated acyl sensor coating.

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8   A method for detection of a controlled substance as described in claim 7
           wherein said acyl-specific controlled substance is a codeine, heroin,
           tetrahydrocannibinol, morphine, psylocibin, amines, alcohols, amphetamines,
           or methamphetamines.

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9   A method for detection of a controlled substance as described in claim 1 or 5
           wherein said step of establishing a spectroscopic sample surface comprises
           the step of establishing a Raman surface.

20 10   A method for detection of a controlled substance as described in claim 9
           wherein said step of establishing a Raman surface comprises the step of
           establishing a Surface Enhanced Raman Scattering surface.

11   A method for detection of an analyte, comprising the steps of:

25   a.   establishing a spectroscopic sample surface;

           b.   placing a diazonium salt sensor coating on said spectroscopic sample
                 surface;

           c.   subjecting said spectroscopic sample surface to at least some
                 diazonium-specific analyte;

30   d.   linking a chemical of said diazonium-specific analyte to said
                 diazonium salt sensor coating on said spectroscopic sample surface;

e.   exposing said diazonium salt sensor coating on said spectroscopic
        sample surface to at least one incident wavelength of energy;

f.   affecting said at least one incident wavelength of energy at least in
        part by said chemical of said diazonium-specific analyte as said
        chemical is linked to said diazonium salt sensor coating on said
5   spectroscopic sample surface to result in a change in intensity of at
        least one wavelength of energy; and

e.   detecting a spectroscopic signal including said change in intensity of
        said at least one wavelength of energy;

g.   spectroscopically analyzing said spectroscopic signal to gain
10   information about said diazonium-specific analyte.

12   A method for spectroscopic analysis of an analyte, comprising the steps of:

a.   establishing a spectroscopic sample surface;

b.   placing a nitroso sensor coating on said spectroscopic sample surface;

15 c.   subjecting said spectroscopic sample surface to at least some nitroso-
        specific analyte;

d.   linking a chemical of said diazonium-specific analyte to said nitroso
        sensor coating on said spectroscopic sample surface;

e.   exposing said nitroso sensor coating on said spectroscopic sample
20   surface to at least one incident wavelength of energy;

f.   affecting said at least one incident wavelength of energy at least in
        part by said chemical of said nitroso-specific analyte as said chemical
        is linked to said nitroso sensor coating on said spectroscopic sample
        surface to result in a change in intensity of at least one wavelength of
25   energy; and

e.   detecting a spectroscopic signal including said change in intensity of
        said at least one wavelength of energy;

g.   spectroscopically analyzing said spectroscopic signal to gain
        information about said nitroso-specific analyte.

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13   A method for spectroscopic analysis of an analyte, comprising the steps of:

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    a.   establishing a spectroscopic sample surface;

    b.   placing an activated acyl sensor coating on said spectroscopic sample surface;

    c.   subjecting said spectroscopic sample surface to at least some acyl-specific analyte;

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    d.   linking a chemical of said acyl-specific analyte to said activated acyl sensor coating on said spectroscopic sample surface;

    e.   exposing said activated acyl sensor coating on said spectroscopic sample surface to at least one incident wavelength of energy;

    f.   affecting said at least one incident wavelength of energy at least in

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part by said chemical of said acyl-specific analyte as said chemical is linked to said activated acyl sensor coating on said spectroscopic sample surface to result in a change in intensity of at least one wavelength of energy; and

    e.   detecting a spectroscopic signal including said change in intensity of

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said at least one wavelength of energy;

    g.   spectroscopically analyzing said spectroscopic signal to gain information about said acyl-specific analyte.

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A method for spectroscopic analysis of an analyte as described in claim 1, 5, 11, 12, or 13 wherein said step of establishing a spectroscopic sample surface comprises the step of establishing a Raman spectroscopic sample surface, wherein said step of exposing said sensor coating on said spectroscopic sample surface to at least one incident wavelength of energy comprises the step of illuminating said spectroscopic sample surface by a Raman

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illumination source to result in a Raman illumination, and wherein said step of affecting said at least one incident wavelength of energy to result in a change in intensity of at least one wavelength of energy comprises the step of Raman scattering said Raman illumination.

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A method for spectroscopic analysis of an analyte as described in claim 14 wherein said step of Raman scattering said Raman illumination comprises

the step of Surface Enhanced Raman Scattering said Raman illumination.

16   A method for detection of a controlled substance as described in claim 14
        and further comprising the step of establishing a modifier which is part of
        said sensor coating wherein said modifier is adapted to influence reactivity

5   between said coating and said controlled substance.

17   A method of spectroscopic analysis of an analyte as described in claim 15
        wherein said step of placing said coating on said spectroscopic sample
        surface comprises the steps of :

10   a.   establishing a surface attachment group attached to said spectroscopic
                sample surface;

        b.   establishing a central molecular scaffolding attached to said surface
                attachment group which is attached to said spectroscopic sample
                surface; and

15   c.   establishing a reactive functional group attached to said central
                molecular scaffolding which is attached to said surface attachment
                group and wherein said reactive functional group is adapted to form a
                covalently bonded adduct with an analyte.

20 18 A method of spectroscopic analysis of an analyte as described in claim 15 wherein
        said step of placing said coating on said spectroscopic sample surface comprises the
        steps of :

        a.   establishing a surface attachment group attached to said spectroscopic
                sample surface which is attached to said spectroscopic sample

25   surface;

        b.   establishing a central molecular scaffolding attached to said surface
                attachment group; and

        c.   establishing a reactive functional group precursor attached to said
                central molecular scaffolding which is attached to said surface

30   attachment group and wherein said reactive functional group
                precursor is adapted to be activated to produce a reactive functional

group to form a covalently bonded adduct with an analyte.

19   A method of spectroscopic analysis of an analyte as described in claim 1, 5, 9, 11, 12, or 13 wherein said step of linking comprises the step of creating covalent bonds with an analyte over a period of time and further comprising

5   the step of washing said coating on said spectroscopic sample surface with a liquid to stop said step of creating covalent bonds with said analyte over a period of time.

20   A method of spectroscopic analysis of an analyte as described in claim 19

10   wherein said step of subjecting said coating on said spectroscopic sample surface also subjects said coating on said spectroscopic sample surface to at least one interfering substance, and wherein said step of washing said coating on said spectroscopic sample surface with a liquid further comprises the step of simultaneously removing said at least one interfering substance from said

15   analyte-reactive coating on said spectroscopic sample surface.

21   A method of spectroscopic analysis of an analyte as described in claim 19 wherein said step of subjecting said coating on said spectroscopic sample surface subjects said coating on said spectroscopic sample surface to excess

20   analyte, and wherein said step of washing said analyte-reactive coating on said spectroscopic sample surface with a liquid further comprises the step of removing said excess analyte from said analyte-reactive coating on said spectroscopic sample surface .

25 22   A method of spectroscopic analysis of an analyte as described in claim 1, 5, 9, 11, 12, or 13 and further comprising the step of establishing a second sensor molecule type on said spectroscopic sample surface.

23   A system for detection of a controlled substance, comprising:

30   a.   a spectroscopic sample surface;

          b.   a diazonium compound sensor coating on said spectroscopic sample

surface wherein said diazonium compound sensor coating is adapted
so as to establish an attachment link between said sensor coating and
a chemical in said controlled substance; and
wherein said attachment link is adapted to retain said chemical in said
controlled substance in a manner which can be spectroscopically sensed.

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24   A system for detection of a controlled substance as described in claim 23
wherein said diazonium compound sensor coating on said spectroscopic
sample surface is adapted to establish a covalent bond as said attachment link
between said coating and said chemical in said controlled substance.

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25   A system for detection of a controlled substance as described in claim 23
and further comprising an adduct formed by said diazonium compound
sensor coating on said spectroscopic sample surface and said chemical in said
controlled substance.

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26   A system for detection of a controlled substance as described in claim 23
wherein said diazonium-specific controlled substance is a codeine, heroin,
psylocibin, tetrahydrocannibinol or morphine.

20 27   A system for detection of a controlled substance, comprising:
        a.   a spectroscopic sample surface;
        b.   an activated acyl sensor coating on said spectroscopic sample surface
                wherein said activated acyl sensor coating is adapted so as to
                establish an attachment link between said sensor coating and a
25   chemical in said controlled substance; and
        wherein said attachment link retains said chemical in said controlled
        substance in a manner which can be spectroscopically sensed.

28   A system for detection of a controlled substance as described in claim 27
30   wherein said activated acyl sensor coating on said spectroscopic sample
        surface is adapted to establish a covalent bond as said attachment link

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between said coating and said chemical in said controlled substance.

29   A system for detection of a controlled substance as described in claim 27 and further comprising an adduct formed by said activated acyl sensor coating on said spectroscopic sample surface and said chemical in said controlled substance.

30   A system for detection of a controlled substance as described in claim 27 wherein said acyl-specific controlled substance is a codeine, heroin, tetrahydrocannibinol, morphine, psylocibin, amines, alcohols, amphetamines, methamphetamines.

31   A system for detection of a controlled substance as described in claim 23 or 27 wherein said spectroscopic sample surface comprises a Raman surface.

32   A system for detection of a controlled substance as described in claim 31 wherein said Raman surface comprises a Surface Enhanced Raman Scattering surface.

33   A system for detection of a controlled substance as described in claim 23 or 27 and further comprising a modifier as part of said coating wherein said modifier is adapted to influence reactivity between said coating and said controlled substance.

34   A system for spectroscopic analysis of an analyte, comprising:

     a.   a spectroscopic sample surface;

     b.   at least one spectroscopic sample location on said spectroscopic surface; and

     c.   a diazonium compound sensor coating at said at least one spectroscopic sample location;

wherein said analyte is a diazonium-specific analyte and wherein said diazonium compound sensor coating is adapted so as to establish an

attachment link between said coating and a chemical in said diazonium-
specific analyte.

35   A system for spectroscopic analysis of an analyte as described in claim 34
wherein said spectroscopic surface comprises a Raman surface.

36   A system for spectroscopic analysis of an analyte as described in claim 34
wherein said diazonium compound sensor coating on said spectroscopic
sample surface is adapted to establish a covalent bond as said attachment link
between said coating and said chemical in said diazonium-specific analyte.

37   A system for spectroscopic analysis of an analyte as described in claim 34
wherein said spectroscopic surface comprises a Surface Enhanced Raman
Scattering surface.

38   A system for spectroscopic analysis of an analyte as described in claim 34
wherein said diazonium compound sensor coating on said spectroscopic
sample surface is adapted to establish a covalent bond as said attachment link
between said coating and an analyte selected from the group of: a cyanide, a
sulphite, a thiol, a sulfonic acid, an amine, an aryl amine, an azide, a carbon
acid, or an electron rich aromatic compound.

39   A system for spectroscopic analysis of an analyte as described in claim 34
wherein said diazonium compound sensor coating on said spectroscopic
sample surface is adapted to establish a covalent bond as said attachment link
between said coating and a blood substance.

40   A system for spectroscopic analysis of an analyte as described in claim 39
wherein said blood substance comprises bilirubin.

41   A system for spectroscopic analysis of an analyte as described in claim 34 or

39 wherein said diazonium compound sensor coating on said spectroscopic sample surface is adapted to establish a covalent bond as said attachment link between said coating and a phenolic compound, a furan, or a pyrrole.

42   A system for spectroscopic analysis of an analyte as described in claim 34, 39 or 41 5   wherein said wherein said diazonium compound sensor coating on said spectroscopic sample surface is adapted to establish a covalent bond as said attachment link between said coating and a heroin, a tetrahydrocannibinol, a morphine, a codeine, or a psylocibin.

10 43   A system for spectroscopic analysis of an analyte, comprising:

    a.   a spectroscopic surface;

    b.   at least one spectroscopic sample location on said spectroscopic surface; and

    c.   a nitroso sensor coating at said at least one spectroscopic sample 15   location;

wherein said analyte is a nitroso-specific analyte and wherein said nitroso sensor coating is adapted so as to establish an attachment link between said coating and a chemical in said nitroso-specific analyte.

20 44   A system for spectroscopic analysis of an analyte as described in claim 43 wherein said spectroscopic surface comprises a Raman surface.

45   A system for spectroscopic analysis of an analyte as described in claim 43 wherein said nitroso sensor coating on said spectroscopic sample surface is 25   adapted to establish a covalent bond as said attachment link between said coating and said chemical in said nitroso-specific analyte.

46   A system for spectroscopic analysis of an analyte as described in claim 43 wherein said spectroscopic surface comprises a Surface Enhanced Raman 30   Scattering surface.

47   A system for spectroscopic analysis of an analyte as described in claim 43
            wherein said nitroso sensor coating on said spectroscopic sample surface is
            adapted to establish a covalent bond as said attachment link between said
            coating and an analyte which is an amine.

5 48   A system for spectroscopic analysis of an analyte, comprising:
            a.   a spectroscopic surface;
            b.   at least one spectroscopic sample location on said spectroscopic
                    surface; and
            c.   an activated acyl sensor coating at said at least one spectroscopic
10   sample location;
            wherein said analyte is an acyl-specific analyte and wherein said activated
            acyl sensor coating is adapted so as to establish an attachment link between
            said coating and a chemical in said acyl-specific analyte.

15 49   A system for spectroscopic analysis of an analyte as described in claim 48
            wherein said spectroscopic surface comprises a Raman surface.

50   A system for spectroscopic analysis of an analyte as described in claim 48
            wherein said activated-acyl sensor coating on said spectroscopic sample
20   surface is adapted to establish a covalent bond as said attachment link
            between said coating and said chemical in said acyl-specific analyte.

51   A system for spectroscopic analysis of an analyte as described in claim 48
            wherein said spectroscopic surface comprises a Surface Enhanced Raman
25   Scattering surface.

52   A system for spectroscopic analysis of an analyte as described in claim 48
            wherein said activated acyl sensor coating on said spectroscopic sample
            surface is adapted to establish a covalent bond as said attachment link
30   between said coating and an analyte which is an alcohol.

53   A system for spectroscopic analysis of an analyte as described in claim 23,
            27, 34, or 35 wherein said coating further comprises a second sensor
            molecule type on said spectroscopic sample surface.

54   A system for spectroscopic analysis of an analyte as described in claim 23,
5   27, 34, or 35 wherein said coating comprises:

   a.   a surface attachment group attached to said spectroscopic sample
            surface;

   b.   a central molecular scaffolding attached to said surface attachment
            group which is attached to said spectroscopic sample surface; and

10 c.   a reactive functional group attached to said central molecular
            scaffolding which is attached to said surface attachment group and
            wherein said reactive functional group is adapted to form a covalently
            bonded adduct with an analyte.

15 55   A system for spectroscopic analysis of an analyte as described in claim 23,
            27, 34, or 35 wherein said coating comprises:

   a.   a surface attachment group attached to said spectroscopic sample
            surface;

   b.   a central molecular scaffolding attached to said surface attachment
20   group which is attached to said spectroscopic sample surface; and

   c.   a reactive functional group precursor attached to said central
            molecular scaffolding which is attached to said surface attachment
            group and wherein said reactive functional group precursor is adapted
            to form a covalently bonded adduct with an analyte.

25

56   A system for spectroscopic analysis of an analyte as described in claim 23,
            34, 35, 37, 39, 43, 44, 46, 48, 49, or 51 and further comprising:

   a.   an illumination device which illuminates said coating on said
            spectroscopic sample surface so as to produce a spectroscopic signal;
30   and

   b.   a sensor positioned so as to receive said spectroscopic signal.

57   A method of spectroscopic analysis of an analyte, comprising the steps of:

            a.   establishing a spectroscopic sample surface;

            b.   placing an analyte-reactive coating on said spectroscopic sample

5   surface;

            c   subjecting said analyte-reactive coating on said spectroscopic sample

                    surface to an analyte;

            d.   permanently bonding said analyte to said analyte-reactive coating on

                    said spectroscopic sample surface;

10   e.   exposing said analyte-reactive coating on said spectroscopic sample

                    surface to at least one incident wavelength of energy;

            f.   affecting said at least one incident wavelength of energy at least in

                    part by said analyte as said analyte is permanently bonded to said

                    analyte-reactive coating on said spectroscopic sample surface to result

15   in a change in intensity of at least one wavelength of energy; and

            g.   spectroscopically analyzing said change in intensity of said at least

                    one wavelength of energy to gain information about said analyte.

58   A method of spectroscopic analysis of an analyte as described in claim 57

20   wherein said step of permanently bonding said analyte to said analyte-

            reactive coating on said spectroscopic sample comprises the step of

            conducting a combination reaction between said analyte and said analyte-

            reactive coating on said spectroscopic sample surface to create an adduct

            having a decomposition rate that is essentially zero.

25 59   A method of spectroscopic analysis of an analyte as described in claim 58

            wherein said step of conducting a combination reaction between said analyte

            and said analyte-reactive coating on said spectroscopic sample surface

            comprises the step of covalently bonding said analyte to said analyte-reactive

            coating on said spectroscopic sample surface.

30

60   A method of spectroscopic analysis of an analyte, comprising the steps of:

a.   establishing a spectroscopic sample surface;

b.   placing an analyte-reactive coating on said spectroscopic sample
      surface;

c   subjecting said analyte-reactive coating on said spectroscopic sample
      surface to an analyte;

5   d.   covalently bonding said analyte to said analyte-reactive coating on
      said spectroscopic sample surface;

e.   exposing said analyte-reactive coating on said spectroscopic sample
      surface to at least one incident wavelength of energy;

f.   affecting said at least one incident wavelength of energy at least in
10   part by said analyte as said analyte is covalently bonded to said
      spectroscopic sample surface to result in a change in intensity of at
      least one wavelength of energy; and

g.   spectroscopically analyzing said change in intensity of said at least
      one wavelength of energy to gain information about said analyte.

15

61   A method of spectroscopic analysis of an analyte as described in claim 60
      wherein said step of affecting said at least one incident wavelength of energy
      at least in part by said analyte comprises the step of producing an adduct-
      specific signal.

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62   A method of spectroscopic analysis of an analyte as described in claim 61
      further comprising the step of substantially detecting an unaltered signal.

63   A method of spectroscopic analysis of an analyte as described in claim 62
25   wherein said step of establishing a spectroscopic sample surface comprises
      the step of establishing a Raman spectroscopic sample surface and wherein
      said step of affecting said at least one incident wavelength of energy at least
      in part by said analyte as it is covalently bonded to said analyte-reactive
      coating on said spectroscopic sample surface to result in a change in intensity
30   of at least one wavelength of energy comprises the step of affecting said at
      least one incident wavelength of energy by Raman scattering.

64   A method of spectroscopic analysis of an analyte as described in claim 60
          wherein said step of placing an analyte-reactive coating on said spectroscopic
          sample surface comprises the step of placing an analyte-reactive compound
          selected from a carbon-containing group.

5   65   A method of spectroscopic analysis of an analyte as described in claim 60
          wherein said step of placing an analyte-reactive coating on said spectroscopic
          sample surface comprises the step of placing an analyte-reactive compound
          selected from a non-protein group.

10 66   A method of spectroscopic analysis of an analyte as described in claim 62 or
          65 wherein said step of covalently bonding said analyte to said analyte-
          reactive coating on said spectroscopic sample surface comprises the step of
          forming a covalently bonded adduct between said analyte and said analyte-
          reactive coating on said spectroscopic sample surface.

15

    67   A method of spectroscopic analysis of an analyte as described in claim 66
          wherein said step of forming a covalently bonded adduct between said
          analyte and said analyte-reactive coating on said spectroscopic sample
          surface comprises the step of forming said covalently bonded adduct between

20   said analyte and an analyte-reactive compound selected from a carbon-
          containing group.

    68   A method of spectroscopic analysis of an analyte as described in claim 66
          wherein said step of forming a covalently bonded adduct between said

25   analyte and said analyte-reactive coating on said spectroscopic sample
          surface comprises the step of forming said covalently bonded adduct between
          said analyte and an analyte-reactive compound selected from a non-protein
          group.

30 69   A method of spectroscopic analysis of an analyte as described in claim 67
          wherein said step of placing an analyte-reactive compound selected from a

carbon-containing group comprises the steps of :

a. establishing a surface attachment group attached to said spectroscopic sample surface;

b. establishing a central molecular scaffolding attached to said surface attachment group which is attached to said spectroscopic sample surface; and

c. establishing a reactive functional group attached to said central molecular scaffolding which is attached to said surface attachment group and wherein said reactive functional group forms said covalently bonded adduct with said analyte.

70   A method of spectroscopic analysis of an analyte as described in claim 69 wherein said step of placing an analyte-reactive compound selected from a carbon-containing group comprises the steps of :

a. establishing a surface attachment group attached to said spectroscopic sample surface which is attached to said spectroscopic sample surface;

b. establishing a central molecular scaffolding attached to said surface attachment group; and

c. establishing a reactive functional group precursor attached to said central molecular scaffolding which is attached to said surface attachment group and wherein said reactive functional group precursor is activated to produce said reactive functional group before forming said covalently bonded adduct with said analyte.

71   A method of spectroscopic analysis of an analyte as described in claim 60 wherein said step of covalently bonding said analyte to said reactive functional group of said analyte-active coating comprises the step of creating covalent bonds between said analyte and said reactive functional group of said analyte-active coating over a period of time and further comprising the

step of washing said analyte-reactive coating on said spectroscopic sample surface with a liquid to stop said step of creating covalent bonds between said analyte and said reactive functional group of said analyte-active coating over a period of time.

5   72   A method of spectroscopic analysis of an analyte as described in claim 71 wherein said step of subjecting said analyte-reactive coating on said spectroscopic sample surface to an analyte also subjects said analyte-reactive coating on said spectroscopic sample surface to at least one interfering substance, wherein said step of covalently bonding said analyte to said

10   reactive functional group of said analyte-active coating comprises the step of creating covalent bonds between said analyte and said reactive functional group of said analyte-active coating over a period of time, and wherein said step of washing said analyte-reactive coating on said spectroscopic sample surface with a liquid comprises the steps of:

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a.   stopping said step of creating covalent bonds between said analyte and said reactive functional group of said analyte-active coating over a period of time; and

b.   simultaneously removing said at least one interfering substance from

20   said analyte-reactive coating on said spectroscopic sample surface.

73   A method of spectroscopic analysis of an analyte as described in claim 71 wherein said step of subjecting said analyte-reactive coating on said spectroscopic sample surface to an analyte also subjects said analyte-reactive

25   coating on said spectroscopic sample surface to excess analyte, wherein said step of covalently bonding said analyte to said reactive functional group of said analyte-active coating comprises the step of creating covalent bonds between said analyte and said reactive functional group of said analyte-active coating over a period of time, and wherein said step of washing said analyte-

30   reactive coating on said spectroscopic sample surface with a liquid comprising the steps of:

        a.   stopping said step of creating covalent bonds between said analyte and said reactive functional group of said analyte-active coating over a period of time; and

        b.   simultaneously removing said excess analyte from said analyte-reactive coating on said spectroscopic sample surface .

5

74   A system for spectroscopic analysis of an analyte, comprising:

        a.   a spectroscopic sample surface;

        b.   an analyte-reactive coating on said spectroscopic sample surface; and

10   c.   a chemical reaction event location on said analyte-reactive coating on said spectroscopic sample surface which is adapted to produce a permanently bonded adduct between an analyte and said analyte-reactive coating on said spectroscopic sample surface.

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75   A system for spectroscopic analysis of an analyte, comprising:

        a.   a spectroscopic sample surface;

        b.   an analyte-reactive coating on said spectroscopic sample surface; and

20   c.   a chemical reaction event location on said analyte-reactive coating on said spectroscopic sample surface which is adapted to produce a covalently bonded adduct between an analyte and said analyte-reactive coating on said spectroscopic sample surface.

25 76   A system for spectroscopic analysis of an analyte as described in claim 75 and further comprising:

        a.   an illumination device which illuminates said analyte-reactive coating on said spectroscopic sample surface so as to produce a spectroscopic signal; and

30   b.   a sensor positioned so as to receive said spectroscopic signal.

77   A system for spectroscopic analysis of an analyte as described in claim 75
      and further comprising an internal standard wherein said internal standard is
      co-located with said chemical reaction event location.

78   A system for spectroscopic analysis of an analyte as described in claim 75 or
5   76 wherein said spectroscopic surface comprises a Raman surface.

79   A system for spectroscopic analysis of an analyte as described in claim 75
      wherein said analyte-reactive coating on said spectroscopic sample surface
      comprises an analyte-reactive compound selected from a carbon-containing
10   group.

80   A system for spectroscopic analysis of an analyte as described in claim 75
      wherein said analyte-reactive coating on said spectroscopic sample surface
      comprises an analyte-reactive compound selected from non-protein
15   molecules.

81   A system for spectroscopic analysis of an analyte as described in claim 75 or
      76 wherein said analyte-reactive coating comprises:
20   a.   a surface attachment group attached to said spectroscopic sample
            surface;
      b.   a central molecular scaffolding attached to said surface attachment
            group which is attached to said spectroscopic sample surface; and
      c.   a reactive functional group attached to said central molecular
25   scaffolding which is attached to said surface attachment group and
            wherein said reactive functional group is adapted to form a covalently
            bonded adduct with said analyte.

82   A system for spectroscopic analysis of an analyte as described in claim 75 or
30   76 wherein said analyte-reactive coating comprises:
      a.   a surface attachment group attached to said spectroscopic sample

surface;

b.   a central molecular scaffolding attached to said surface attachment group which is attached to said spectroscopic sample surface; and

c.   a reactive functional group precursor attached to said central molecular scaffolding which is attached to said surface attachment

5   group and wherein said reactive functional group precursor is adapted to be activated to become said chemical reaction event location.

83   A method for spectroscopic analysis of an analyte, comprising the steps of :

a.   establishing a surface attachment group attached to a spectroscopic

10   sample surface;

b.   establishing a central molecular scaffolding attached to said surface attachment group; and

c.   establishing a reactive functional group attached to said central molecular scaffolding wherein said reactive functional group is

15   adapted to form a covalent bond with an analyte.

84   A method for spectroscopic analysis of an analyte as described in claim 83 wherein said step of establishing a reactive functional group attached to said central molecular scaffolding wherein said reactive functional group is

20   adapted to form a covalent bond with an analyte comprises the step of adapting said reactive functional group to form an adduct between said reactive functional group and said analyte.

85   A method for spectroscopic analysis of an analyte as described in claim 83

25   wherein said step of establishing a central molecular scaffolding attached to said surface attachment group comprises the step of establishing a monocyclic aromatic ring, a polycyclic aromatic ring, a heteroaromatic ring, or a non-aromatic scaffolding attached to said surface attachment group.

30 86   A method for spectroscopic analysis of an analyte as described in claim 83 wherein said step of establishing a reactive functional group attached to said

central molecular scaffolding comprises the step of establishing a diazonium group, a diazonium salt, a nitroso, an activated acyl group, an electrophilic carbon, or a carbonyl attached to said central molecular scaffolding.

87   A method for spectroscopic analysis of an analyte, comprising the steps of:

5   a.   establishing a surface attachment group attached to a spectroscopic sample surface;

        b.   establishing a central molecular scaffolding attached to said surface attachment group; and

        c.   establishing a reactive functional group precursor attached to said

10   central molecular scaffolding wherein said reactive functional group precursor is adapted to be activated to form a reactive functional group;

        d.   activating said reactive functional group precursor to form said reactive functional group; and

15   e.   covalently bonding said reactive functional group with an analyte.

88   A method for spectroscopic analysis of an analyte as described in claim 87 wherein said step of activating said reactive functional group precursor to form said reactive functional group comprises the step of subjecting said

20   reactive functional group precursor to an activation substance which activates said reactive functional group precursor to become said reactive functional group.

89   A method for spectroscopic analysis of an analyte as described in claim 88

25   wherein said step of covalently bonding said reactive functional group with an analyte comprises the step of forming an adduct with said analyte.

90   A method for spectroscopic analysis of an analyte as described in claim 83 or 87 and further comprising the step of establishing an internal standard on

30   said spectroscopic sample surface wherein said internal standard is co-located with said adduct.

91   A method for spectroscopic analysis of an analyte as described in claim 90 said step of establishing an internal standard on said spectroscopic sample surface wherein said internal standard is co-located with said adduct comprises the step of establishing a tether which links said surface attachment group to said central molecular scaffolding.

5 .

92   A method for spectroscopic analysis of an analyte as described in claim 90 wherein said steps of establishing a surface attachment group and establishing a central molecular scaffolding form at least part of a coating and wherein said step of establishing an internal standard on said

10   spectroscopic sample surface wherein said internal standard is co-located with said adduct comprises the step of establishing a non-carbon structure, a nitro group, a sulfonyl group, a carbon structure, or a carbonyl group incorporated as part of said coating.

15 93   A method for spectroscopic analysis of an analyte as described in claim 83 or 87 wherein said steps of establishing a surface attachment group and establishing a central molecular scaffolding form at least part of a coating and further comprising the step of establishing a modifier which influences the reactivity of said reactive functional group.

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94   A method for spectroscopic analysis of an analyte as described in claim 93 wherein said step of establishing said modifier comprises the step of establishing a halide, an electron-donating group, an alkoxy group, amide group, amino group, an electron-withdrawing group, a nitro group, a

25   carboxlic acid group, an ester group, a sulfoxide group, or a sulfone group on said spectroscopic surface.

95   A system for spectroscopic analysis of an analyte, comprising:
            a.   a spectroscopic sample surface; and

30   b.   an analyte-reactive coating comprising:
                  1)   a surface attachment group;

2)   a central molecular scaffolding attached to said surface
        attachment group; and

3)   a reactive functional group attached to said central molecular
        scaffolding wherein said reactive functional group is adapted
        to be attached to an analyte by a covalent bond.

5

96   A system for spectroscopic analysis of an analyte as described in claim 95
        wherein said central molecular scaffolding attached to said surface
        attachment group comprises a monocyclic aromatic ring, a polycyclic
        aromatic ring, a heteroaromatic ring, or a non-aromatic scaffolding.

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97   A system for spectroscopic analysis of an analyte as described in claim 95
        wherein said reactive functional group attached to said central molecular
        scaffolding comprises a diazonium group, a diazonium salt, a nitroso, an
        activated acyl sensor, an electrophilic carbon, or a carbonyl.

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98   A system for spectroscopic analysis of an analyte, comprising:

        a.   a spectroscopic sample surface; and
        b.   an analyte-reactive coating comprising :

20   1)   a surface attachment group;

                2)   a central molecular scaffolding attached to said surface
                        attachment group; and

                3)   a reactive functional group precursor attached to said central
                        molecular scaffolding wherein said reactive functional group

25   precursor is adapted to be activated to become a reactive
                        functional group attached to said central molecular scaffolding
                        and wherein said reactive functional group attached to said
                        central molecular scaffolding is adapted to form a covalent
                        bond with said analyte.

30

99   A system for spectroscopic analysis of an analyte as described in claim 98

and further comprising an activation substance which activates said reactive
functional group precursor to become said reactive functional group.

100   A system for spectroscopic analysis of an analyte as described in claim 99
        wherein said reactive functional group precursor forms an adduct with said
        analyte after its activation by said activation substance.

101   A system for spectroscopic analysis of an analyte as described in claim 95 or
        98 and further comprising an internal standard wherein said internal standard
        is co-located with said adduct.

102   A system for spectroscopic analysis of an analyte as described in claim 101
        wherein said internal standard comprises a tether.

103   A system for spectroscopic analysis of an analyte as described in claim 101
        wherein said surface attachment group and said central molecular scaffolding
        form at least part of a coating, and wherein said internal standard comprises a
        non-carbon structure, a nitro group, a sulfonyl group, a carbon structure, or a
        carbonyl group incorporated as part of said coating.

104   A system for spectroscopic analysis of an analyte as described in claim 95 or
        98 and further comprising a modifier which is incorporated as part of said
        analyte-reactive coating wherein said modifier is adapted to influence
        reactivity between said coating and said analyte.

105   A system for spectroscopic analysis of an analyte as described in claim 104
        wherein said modifier comprises a halide, an electron-donating group, an
        alkoxy group, amide group, amino group, an electron-withdrawing group, a
        nitro group, a carboxlic acid group, an ester group, a sulfoxide group, or a
        sulfone group.

106   A method of spectroscopic analysis of an analyte, comprising the steps of:

a.   establishing a first sensor molecule type on a spectroscopic
        sample surface;

b.   establishing a second sensor molecule type on said
        spectroscopic sample surface;

c.   subjecting said spectroscopic sample surface to an analyte;

5   d.   interacting said analyte with said first sensor molecule type;

e.   interacting said analyte with said second sensor molecule
        type;

f.   exposing said spectroscopic sample surface to at least one
        incident wavelength of energy;

10   g.   affecting said at least one incident wavelength of energy at
        least in part by said analyte to result in a change in intensity of
        at least one wavelength of energy; and

h.   spectroscopically analyzing said change in intensity of said at
        least one wavelength of energy to gain information about said

15   analyte.

107   A method of spectroscopic analysis of an analyte as described in claim 106
        wherein said step of interacting said analyte with said first sensor molecule
        type comprises the step of forming a covalent bond between said analyte and
20   said first sensor molecule type.

108   A method of spectroscopic analysis of an analyte as described in claim 107
        wherein said step of interacting said analyte with said second sensor
        molecule type comprises the step of forming a covalent bond between said
25   analyte and said second sensor molecule type.

109   A method of spectroscopic analysis of an analyte as described in claim 106
        wherein said step of establishing said first sensor molecule type on said
        spectroscopic sample surface comprises the step of establishing said first
30   sensor molecule type on a Raman surface.

110   A method of spectroscopic analysis of an analyte as described in claim 109 wherein said step of establishing said second sensor molecule type on said spectroscopic sample surface comprises the step of establishing said second sensor molecule type on said Raman surface.

5 111   A method of spectroscopic analysis of an analyte as described in claim 110 wherein said steps of establishing said first and second sensor molecule types on said Raman surface comprise the steps of establishing said first and second sensor molecule types on a Surface Enhanced Raman Scattering surface.

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112   A method of spectroscopic analysis of an analyte as described in claim 106 wherein said steps of establishing said first and second sensor molecule types on said spectroscopic sample surface comprise the steps of establishing first and second sensor molecule types which respond to different concentration

15   ranges.

113   A method of spectroscopic analysis of an analyte as described in claim 112 wherein said steps of establishing first and second sensor molecule types which respond to different concentration ranges comprise the step of

20   establishing an overlap region created by said first and second sensor molecule types.

114   A method of spectroscopic analysis of an analyte as described in claim 113 wherein said first sensor molecule type has a first saturation level for a

25   specific analyte, wherein said second sensor molecule type has a second saturation level for said specific analyte, and further comprising the step of establishing different saturation levels for said first and second sensor molecule types.

30 115   A method of spectroscopic analysis of an analyte as described in claim 114 wherein said step of establishing different saturation levels for said first and

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second sensor molecule types comprises the step of establishing
complementary ranges provided by said first and second sensor molecule
types.

116   A method of spectroscopic analysis of an analyte as described in claim 106
5   and further comprising the steps of:

a.   establishing a first modifier attached to said first sensor molecule type
     on said spectroscopic sample surface; and

b.   establishing a second modifier attached to said second sensor
     molecule type on said spectroscopic sample surface.

10

117   A method of spectroscopic analysis of an analyte as described in claim 116
wherein said steps of establishing a first and a second modifiers attached to
said first and said second sensor molecules comprise the steps of establishing
a halide, an electron-donating group, an alkoxy group, amide group, amino
15   group, an electron-withdrawing group, a nitro group, a carboxlic acid group,
an ester group, a sulfoxide group, or a sulfone group attached to said first and
said second sensor molecule types on said spectroscopic sample surface.

118   A method for spectroscopic analysis of multiple species of analytes,
20   comprising the steps of:

a.   establishing a first sensor molecule type on a spectroscopic sample
     surface;

b.   establishing at least a second sensor molecule type on said
     spectroscopic sample surface;

25   c.   subjecting said spectroscopic sample surface to at least a first species
         of analyte wherein a first species of said analytes has a specificity for
         said first sensor molecule type on said spectroscopic sample surface;

d.   interacting said first species of said analytes with said first sensor
     molecule type;

30   e.   exposing said spectroscopic sample surface to at least one incident
         wavelength of energy;

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f.   affecting said at least one incident wavelength of energy at least in
       part by said at least said first species of analyte to result in a change
       in intensity of at least one wavelength of energy; and

h.   spectroscopically analyzing said change in intensity of said at least
       one wavelength of energy to gain information about said first species

5   of said analyte.

119   A method for spectroscopic analysis of multiple species of analytes as
       described in claim 118 and further comprising the steps of:

a.   subjecting said spectroscopic sample surface to at least a second

10   species of analyte wherein a second species of said analyte has a
       specificity for said second sensor molecule type on said spectroscopic
       sample surface;

b.   interacting said second species of said analyte with said second
       sensor molecule type;

15 c. affecting said at least one incident wavelength of energy at least in
       part by said second species of analyte to result in a change in intensity
       of at least one wavelength of energy; and

d.   simultaneously spectroscopically analyzing said change in intensity of
       said at least one wavelength of energy due to said second species of

20   analyte to gain information about said second species of said analyte.

120   A method for spectroscopic analysis of multiple species of analytes as
       described in claim 118 wherein said step of interacting said first species of
       said analytes with said first sensor molecule type comprises the step of

25   forming a first adduct type between said first species of said analytes and said
       first sensor molecule type.

121   A method for spectroscopic analysis of multiple species of analytes as
       described in claim 119 wherein said step of interacting said first species of

30   said analytes with said first sensor molecule type comprises the step of
       forming a first adduct type between said first species of said analytes and said

first sensor molecule type, and wherein said step of interacting said second species of said analytes with said second sensor molecule type comprises the step of forming a second adduct type between said second species of said analytes and said second sensor molecule type.

122   A method for spectroscopic analysis of multiple species of analytes as described in claim 119 wherein said step of spectroscopically analyzing said change in intensity of at least one wavelength of energy to gain information about said two different species of said analytes comprises the step of differentiating information between said first and second different species of said analytes.

123   A method for spectroscopic analysis of multiple species of analytes as described in claim 122 wherein said step of differentiating said at least two different species of analytes comprises the step of quantitating said at least two different species of said analytes.

124   A system for spectroscopic analysis of an analyte, comprising:

      a.   a spectroscopic sample surface;
      b.   a first sensor molecule type on said spectroscopic sample surface; and
      c.   a second sensor molecule type on said spectroscopic sample surface.

125   A system for spectroscopic analysis of an analyte as described in claim 124 wherein said first sensor molecule type comprises a first sensor molecule type which is adapted to form a covalent bond between itself and an analyte when said analyte is subjected to said spectroscopic sample surface.

126   A system for spectroscopic analysis of an analyte as described in claim 125 wherein said second sensor molecule type comprises a second sensor molecule type which is adapted to form a covalent bond between itself and an analyte when said analyte is subjected to said spectroscopic sample

surface.

127   A system for spectroscopic analysis of an analyte as described in claim 124
         wherein said first sensor molecule type on said spectroscopic sample surface
         comprises a Raman sensor molecule type and wherein said spectroscopic

5   sample surface comprises a comprises a Raman surface.

128   A system for spectroscopic analysis of an analyte as described in claim 124
         or 127 wherein said second sensor molecule type on said spectroscopic
         sample surface comprises a Raman sensor molecule type and wherein said

10   spectroscopic sample surface comprises a comprises a Raman surface.

129   A system for spectroscopic analysis of an analyte as described in claim 127
         wherein said spectroscopic sample surface comprises a Surface Enhanced
         Raman Scattering surface.

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130   A system for spectroscopic analysis of an analyte as described in claim 128
         wherein said spectroscopic sample surface comprises a Surface Enhanced
         Raman Scattering surface.

20 131   A system for spectroscopic analysis of an analyte as described in claim 124
         wherein said first and second sensor molecule types on said spectroscopic
         sample surface comprise first and second sensor molecule types which have
         different concentration ranges for a given analyte.

25 132   A system for spectroscopic analysis of an analyte as described in claim 131
         wherein said different concentration ranges of said first and second sensor
         molecule types on said spectroscopic sample surface have an overlap region.

133   A system for spectroscopic analysis of an analyte as described in claim 132
30   wherein said first sensor molecule type has a first saturation level for a
         specific analyte, wherein said second sensor molecule type has a second

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saturation level for said specific analyte, and wherein said first and second saturation levels are different.

134   A system for spectroscopic analysis of an analyte as described in claim 124 wherein said first sensor molecule type has a first analytical range, wherein said second sensor molecule type has a second analytical range, and wherein said first analytical range and said second analytical range are complementary.

135   A system for spectroscopic analysis of an analyte as described in claim 124 and further comprising:

a.   a first modifier attached to said first sensor molecule type on said spectroscopic sample surface; and

b.   a second modifier attached to said second sensor molecule type on said spectroscopic sample surface.

136   A system for spectroscopic analysis of an analyte, comprising:

a.   a spectroscopic sample surface;

b.   a first sensor molecule type on said spectroscopic sample surface wherein said first sensor molecule type responds to a first type of analyte; and

c.   at least one sensor molecule type on said spectroscopic sample surface wherein said second sensor molecule type responds to a second type of analyte, and

wherein said first type of analyte and said second type of analyte are different.

137   A system for spectroscopic analysis of an analyte as described in claim 136 wherein said first sensor molecule type on said spectroscopic sample surface is adapted to bond with a first type of analyte to form a first type of adduct for spectroscopic analysis.

138   A system for spectroscopic analysis of an analyte as described in claim 136
        wherein said second sensor molecule type on said spectroscopic sample
        surface is adapted to bond with a second type of analyte to form a second
        type of adduct for spectroscopic analysis.
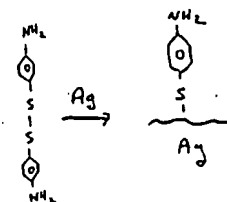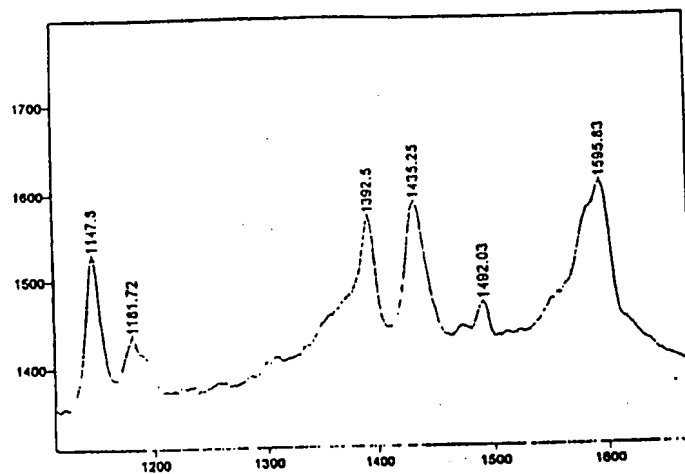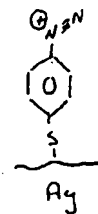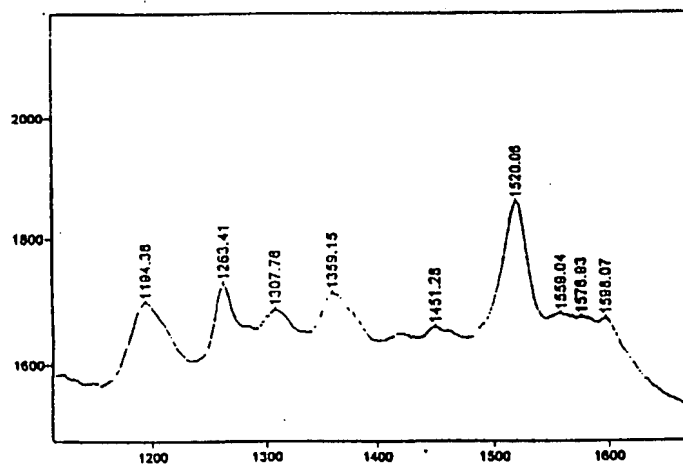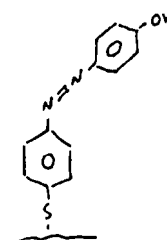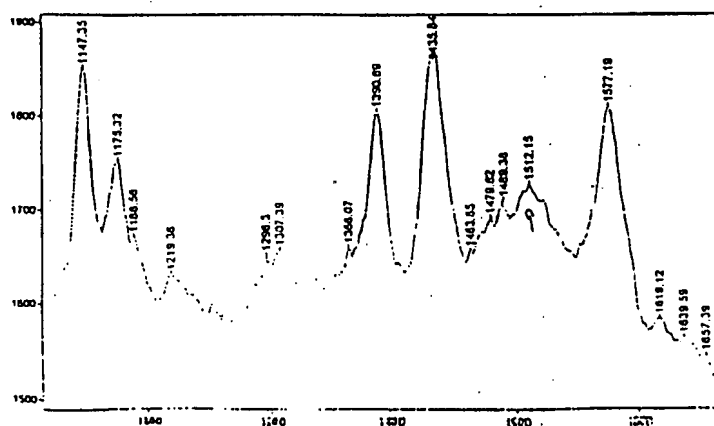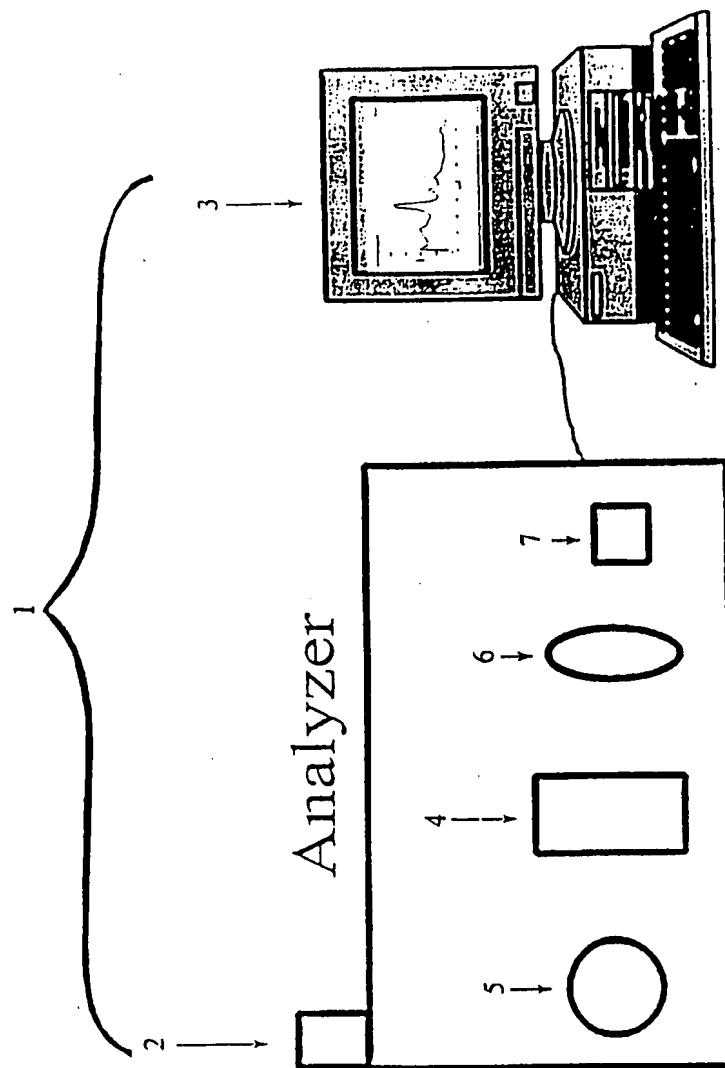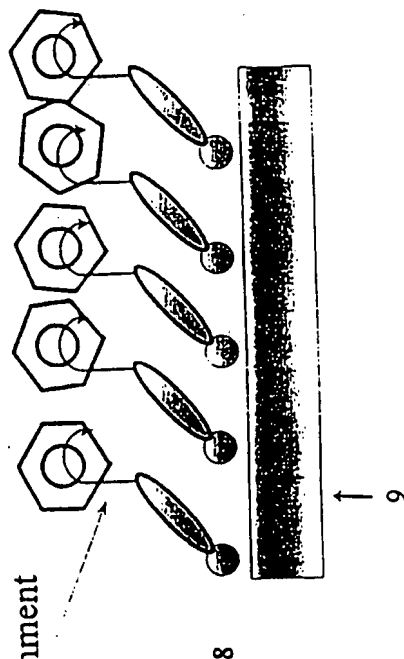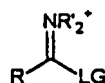
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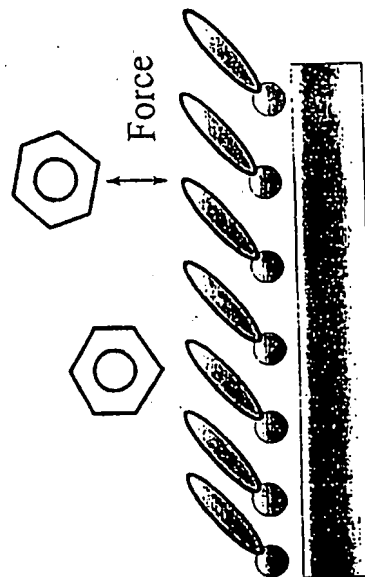
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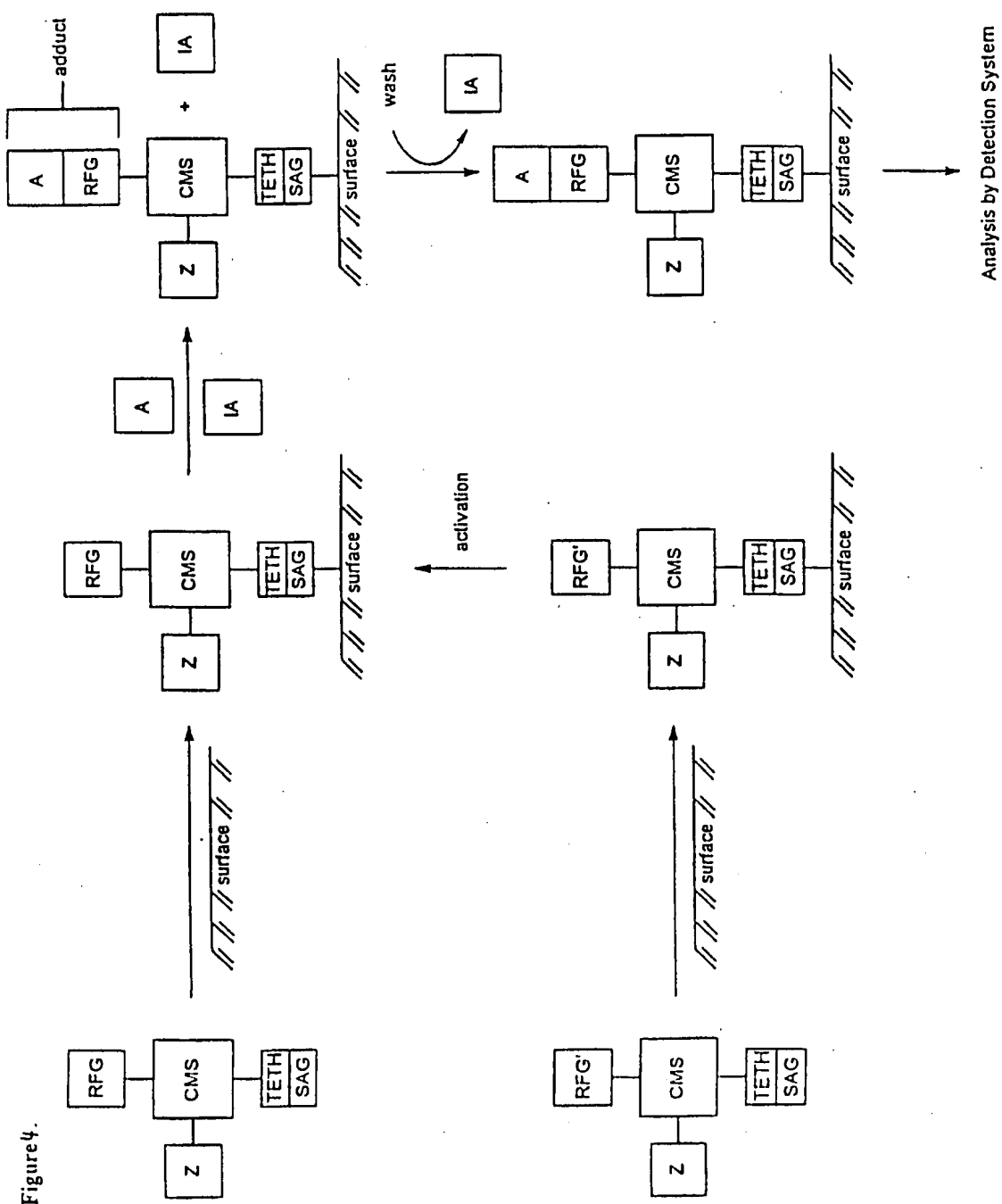
Figure 3

Figure 4.

Figure 5.

Activated Carbonyl Group	Adduct Structure after reaction with RXH	Abbreviations
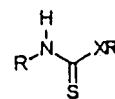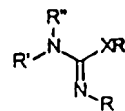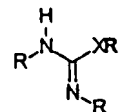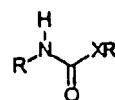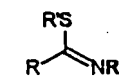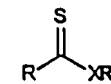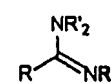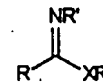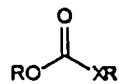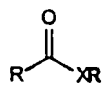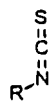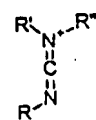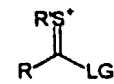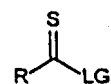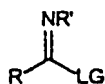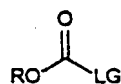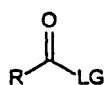
LG = halide, N_3, OSO_2R, OPO_3R_2, OOCR, pyridinium (and derivatives), imidazole (and derivatives), imidazolium (and derivatives)

RXH = [analyte]OH, [analyte]NHR'''

R, R', R'' in activated acyl group = central molecular scaffolding with modifiers, tether, SAG

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6)   :G01N 21/65
US CL   :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :   422/68.1, 82.05, 82.06, 82.09, 82.11; 356/301; 436/86, 91, 92, 93, 96, 98, 104, 107, 815, 816, 901

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,327,211 A (CARRON et al) 05 July 1994 (05-7-94), see entire document.	1-138
Y	US 5,576,216 A (PATCHORNIK) 19 November 1996 (19-11-96), see entire document.	1-138
Y	J. B. Heyns et al, "SERS Study of the Interaction of Alkali Metal Ions with Thiol-Derivatized Dibenzo-18-Crown-6" Analytical Chemistry May 1994, Vol. 66, No. 9, pages 1572 - 1574, see entire document.	1-138
Y	S. M. Angel et al, "Development of a Drug Assay Using Surface-Enhanced Raman Spectroscopy" SPIE 1990, Vol. 1201, pages 469 - 473, see entire document.	1-138

[X] Further documents are listed in the continuation of Box C.   [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"B"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 SEPTEMBER 1998	13 OCT 1998

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ARLEN SODERQUIST
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0661

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/12974

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	R. J. Lacey, "Some Advances in the Use of Raman Spectroscopy in Security Screening Applications" IEE Conference Publication April 1997, Vol. 437, pages 10 - 12, see entire document.	1-138
A	P. R. Carey et al, "Resonance Raman Labels: A Submolecular Probe for Interactions in Biolchemical and Biological Systems" Accounts of Chemical Research 1978, Vol. 11, pages 122 - 128.	1-138
A	E. L. Torres et al, "Trace Determination of Nitrogen-Containing Drugs by Surface Enhanced Raman Scattering Spectroscopy on Silver Colloids" Analytical Chemistry July 1987, Vol. 59, No. 13, pages 1626 - 1632.	1-138
A	K. I. Mullen et al, "Trace Detection of Ionic Species with Surface Enhanced Raman Spectroscopy" Spectroscopy June 1992, Vol. 7, No. 5, pages 24 - 31.	1-138
A	L. M. Cabalin et al, "Surface-Enhanced Raman Spectrometry for Detection in Liquid Chromatography Using a Windowless Flow Cell" Talanta 1993, Vol. 40, No. 11, pages 1741 - 1747.	1-138
A	J. M. E. Storey et al, Applications of Surface-Enhanced Raman Scattering (SERS) to Chemical Detection" Spectroscopy March/April 1995, Vol. 10, No. 3, pages 20 - 25.	1-138
A	E. A. Wachter et al, "Hybrid Substrates for Real-Time SERS-Based Chemical Sensors" Applied Spectroscopy 1995, Vol. 49, No. 2, pages 193 - 199.	1-138

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

422/68.1, 82.05, 82.06, 82.09, 82.11; 356/301; 436/86, 91, 92, 93, 96, 98, 104, 107, 815, 816, 901

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

STN search in CA, BIOSIS, and MEDLINE files
search terms: raman, ser, drug, control?, substance, covalent, detect?, determin?, monitor?, anal?, measur?, test?, sens?, bind?, bond?, react?, bound, immobiliz?